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Role of Aromatase Inhibitors in Breast Cancer for Post Menopausal Women

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ABSTRACT

Worldwide Breast cancer is the most commonly diagnosed disease in women mostly in post menopausal women. Excessive exposure to estrogen and progesterone plays significant role in the etiology of breast carcinoma and biosynthesis pathway of estrogen. Aromatase or CYP19A1 is the main enzyme involved in estrogen biosynthesis. Aromatase belongs to the cytochrome P450 family and is predominantly located in the liver, adrenal gland and fatty tissues. Aromatase inhibitors have been approved as a first line endocrine therapy for postmenopausal women with hormone sensitive and metastatic breast cancer. AIs are used worldwide by many patients in the treatment of breast cancer. It is estimated by many surveys that breast cancer is the main cause of death in post menopausal women. AIs are given in combination with various drugs for the prevention of early stage breast tumor in both post menopausal and menopausal women. In search of potent aromatase inhibitor, molecular docking studies were performed in exemestane (third generation) aromatase inhibitor.

Key words: Breast cancer, Aromatase inhibitors (AIs), post menopausal women, CYP450, Estrogen, CYP19A1.

INTRODUCTION:

ANATOMY AND STRUCTURE OF BREAST

Each of the breasts in both males and females has **nipple** surrounded by a circular, pigmented area called the **areola**.

Breast also called as **mammary glands** because they produce milk, consisting of usually 15–20 glandular lobes which are covered by adipose tissues. Each lobe posses a single **lactiferous duct** that opens to the surface of the nipple.

The ducts of each lobe are divided into several smaller ducts, which originates from **lobules,** within a lobule, the ducts branch and become even smaller, in the milk-producing, or lactating, mammary gland; the ends of these small ducts enlarge to form duct sacs called **alveoli.**

Alveoli are adjoining by the **Myoepithelial cells** and connect to drum out milk from the alveoli. The breasts are supported by suspensory ligaments that reach out from the fascia over the pectoral which is the major muscle to the skin over the breasts. Muscles lie under each breast and cover the ribs.

Further each breast contains blood vessels and also lymph carrying vessels. The lymph vessels divide into small bean-shaped organs called lymph nodes. These lymph nodes are found in clusters (mass) under the arm, above the collarbone, and in the chest. [1, 2]

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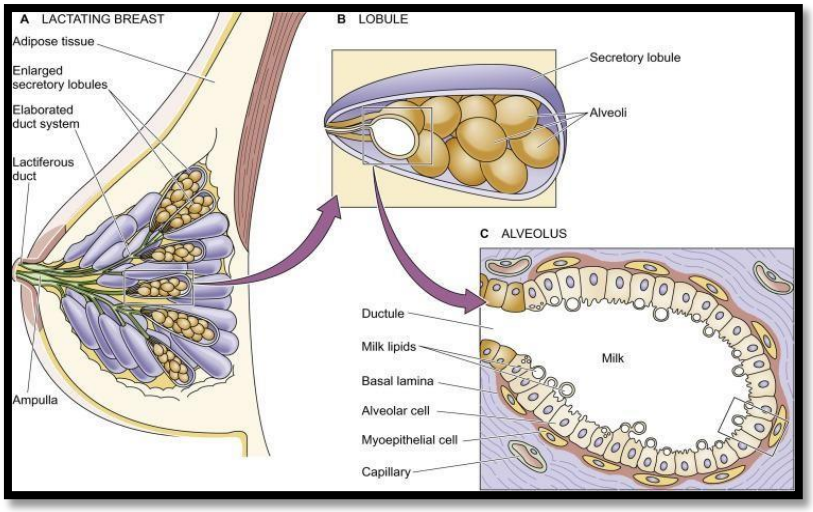

Fig: 1 Breast development- an overview
Source: sciencedirect.com [2]

NEUROENDOCRINE CONTROL OF BREAST DEVELOPMENT AND FUNCTION:-

The hypothalamus stimulates the pituitary gland for the secretion of luteinizing hormone(LH) also known as gonadotropin-releasing hormone (GnRH) and follicle-stimulating hormone (FSH). Than thyrotrophic-releasing hormone(TRH) releases from the hypothalamus which stimulates the secretion of prolactin(PRL),against the inhibitory control of dopamine from the hypothalamus. The pituitary gonadotropin stimulates ovarian synthesis and the release of hormones such as progesterone and estrogen from the corpus luteum, which are responsible for the growth of mammary glands or lactation (mammotrophic effects).In Pregnant women the secretion of estrogen and progesterone enhances during the first 12weeks and afterwards from the placenta. After delivery, polactin secretion increases in women and the breastfeeding let-down reflex, also called the milk- ejection reflex (MER). [3,4,5,6]

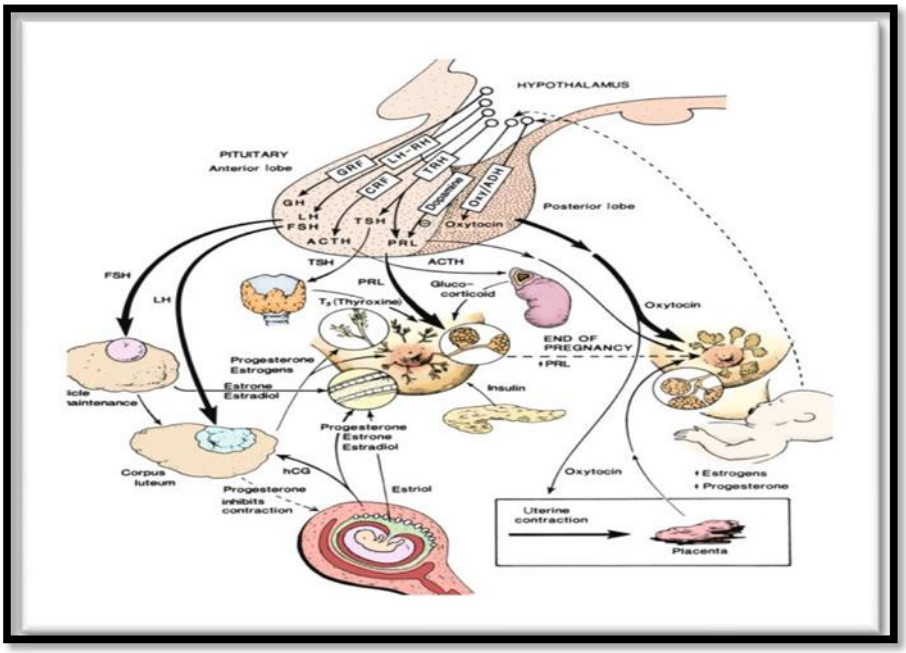

Fig 2: breast physiology: normal and abnormal development and function
Source: sciencedirect.net [7]

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WHAT IS CANCER

- The body is made up of any types of cells. In our body normally cells grow, divide and then die. Sometimes, cells mutate and begin to grow and divide more rapidly than a normal cell rather than dying or we can say cancer is a group of disease causing cells in the body to change and proliferate beyond any control. Most types of cancer cells eventually form a cluster or mass called a tumor.
- If these tumors are cancerous (malignant tumor) they can capture and kill body's healthy tissues or cells. These tumors or cancer cells can metastasize (spread) and form new tumor in other body parts. By contrast, noncancerous tumors (benign tumor) do not spread to the other parts of the body.
- Cancer is a second leading cause of death worldwide after heart diseases, accounting for 8.8 million deaths in 2015. [8,9]
- In Many surveys it is found that globally nearly 1 in 6 deaths is due to cancer. By 2020, the world population is expected to have increases 7.5 billion; of this number, approximately 15 million new cancer cases will be diagnosed, and 12 million cancer patients will die.
- The most common cause of cancer death are cancer of; Lung, Liver, Colorectal, Stomach and Breast.[10,11]

MODE OF TREATMENT

There are many types of cancer treatments available. Treatment is mostly depending on the type of cancer and its stages. Cancer is treated by the following methods:

- Surgery
- Radiation therapy
- Hormone therapy
- Stem cell transplant
- Targeted therapy.[12-19]

BREAST CANCER

- Breast cancer is one of the most commonly distinguish types of cancer in women, extending high occurrence in developed regions of the world compared with developing ones.
- In postmenopausal women, hormone responsive cancers i.e. tumors that indicate estrogen receptors (ER) and progesterone receptors (PgR) indicate about 2-3rd of all breast cancers. In these patients, estrogen is a dominant stimulus for the proliferation and progression of tumor cells. [12,13]
- Two different strategies have been developed to reduce the effect of estrogen on tumor growth:
  - blockage of estrogen binding with targeted receptor
  - Reduction of estrogen circulating levels.

- Breast cancer is associated in the breast tissues, which contains mammary glands for milk production, called lobules, and the ducts that connect the lobules to the nipple.
- Rest of the breast is made up of fatty tissues, connective tissues, and lymphatic tissues.
- Breast cancer is generally diagnosed during a screening examination, before or after symptoms have developed, when a woman feels a lump.
- Cluster is seen on a mammogram and most breast lumps turn out to be benign which are non-cancerous lumps that nor grow neither spread, and are not life-threatening.

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- If any cancerous cell is suspected after a clinical breast examination or imaging, than microscopic analysis of breast tissues is absolute necessity.
- This will provide an absolute diagnosis and also help to determine the growth of cancer (in situ or invasive) and to characterize the pattern of the cancerous cell.
- The tissue for microscopic analysis can be obtained via surgical biopsy. Biopsy is based on individual patient's clinical factors and availability of particular biopsy devices, and resources.
- Benign tumor in particularly, known as a fibro adenoma, is common in young women. Infection of the breast tissue can also occur during breastfeeding. **Mammitis** is the term used for the inflammation of breast.[20,21]

General Types of Breast Cancer

There are several types of breast cancer depend on where in the site of its emergence, which are as follows:

- Ductal Carcinoma in Situ (DCIS)
- Invasive Breast Cancer (IDC/ILC)
- Triple-negative Breast Cancer
- Angiosarcoma of the Breast
- Inflammatory Breast Cancer
- Paget Disease of the Breast [22,23]

AROMATASE INHIBITORS

However aromatase has some features in common with other CYP450 enzymes, according to the sequence analysis near the heme binding region shows only in the range of 17.9 – 23.5 % with other steroidogenic P450 enzymes. This indicates that aromatase CYP450) belongs to a separate gene family, which has been intended as CYP19. [24,25]

Estrogens are generally known as the female sex hormones, primarily responsible for sexual progression in women.

For example:-Estrogens play an essential role in metabolic process of bones and lipids. Further, they are prestigious for their role in the natural history of diseases associated with ovarian and uterus carcinoma.

Hormone sensitivity breast cancer is associated with estrogen, related to hormonal irregularities including neoplasia of breast and has been build to enhance with the age of patient, leading to its significant occurrence among postmenopausal women compared to the younger ones. In spite of the fact that the ovaries no longer produces estrogens after menopause, the synthesis of estrogen is increases in peripheral tissues including skin, adipose tissue and breast.[25,26,27]

TYPES OF AROMATASE INHIBITORS

Aromatase enzyme inhibitors may be divided into two main classes which are as follows:-

Type I Aromatase inhibitors interact with the substrate binding sites of the enzyme. Structure of most of them is similar to androgens and they may have significant hormonal activity.

Type II Aromatase inhibitors interact with the heme moiety of the CYP450 prosthetic group of the aromatase molecule. These inhibitors contain affirmative positioned heteroatoms, usually in the imidazole and triazole ring, which facilitate them to bind with CYP450 enzymes such that their heteroatom's co-ordinate with the heme moiety.[28,29,30]

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ROLE OF AROMATASE INHIBITORS IN BREST CANCER:

- The estrogen inhibitors contend with endogenous estrogen for the binding to their receptor. Tamoxifen is the most commonly used drug both for pre-and postmenopausal women.
- Prolonged exposure to estrogen and progesterone plays a significant role in the etiology of breast carcinoma and biosynthesis pathway of estrogen is thus an important therapeutic target. The main enzyme involved in estrogen biosynthesis is CYP19A1 or aromatase that belongs to the cytochrome P450 family and is substantially located in the liver, adrenal gland and fatty tissue. [29,30]
- However, the source of estrogen differs widely between premenopausal and postmenopausal women. In premenopausal women, the main source of estrogen is the ovary, while in postmenopausal women; estrogen is acquired from the conversion of androgens into estrogens (through the aromatase enzyme). Therefore, the aromatase enzyme directly affects biosynthesis of estrogen in the breast and it is believed that this enzyme plays an important role in the progression of breast cancer.
- According to the clinical studies AIs have been recently approved as a potent endocrine therapy for postmenopausal women among hormone-sensitive and metastatic breast cancer. There are two types of AIs categorized as steroidal inhibitors (type I) and non steroidal inhibitors (type II).
- Exemestane, letrozol and anastrozole, are the most widely recommended drugs, due to their inflated selectivity and slighter adverse effects for the aromatase enzyme as compared with the previous generations of AIs.
- Exemestane is a type I inhibitor, contains steroidal moiety that forms covalent bonds with enzyme, and this is irreversible inhibition and can only be controlled by the synthesis of a new enzyme. [30,31,32]

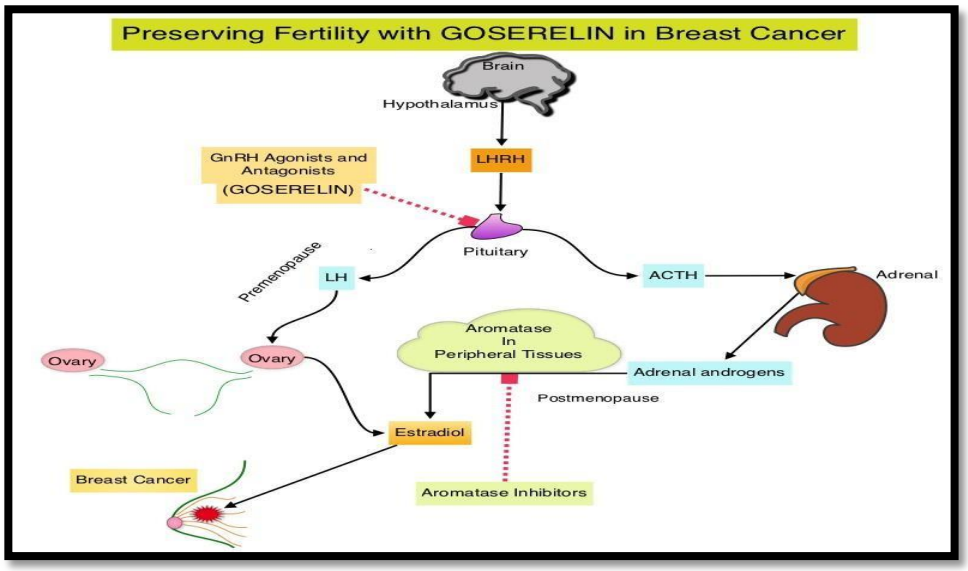

Fig 3: Estrogen production in premenopausal and postmenopausal women.
LH: luteinizing hormone; FSH: follicle-stimulating hormone.
Source: Oncoprescribe.com [33]

MECHANISM OF ACTION

Aromatase is a protein and redox partner composite, the functions of aromatse in alliance with NADPH (Nicotinamide adenine dinucleotide phoshate) dependent reductase. NADPH is

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involved in the conversion of androstenedione and testosterone in to estrone and estradiol respectively. Estradiol, is the most potent endogenous hormone, which is biosynthesized out of androgens through CYP450 enzyme complex called aromatase.

Aromatase Inhibitors act by blocking the activity of cytochrome P-450-enzyme i.e. aromatase which promotes the conversion of androstenedione and testosterone to estrone and estradiol respectively in postmenopausal women, likely in adipose tissue, liver, muscle, and brain and breast cancer tissue thereby reducing estrogen circulating levels.[32,33,34]

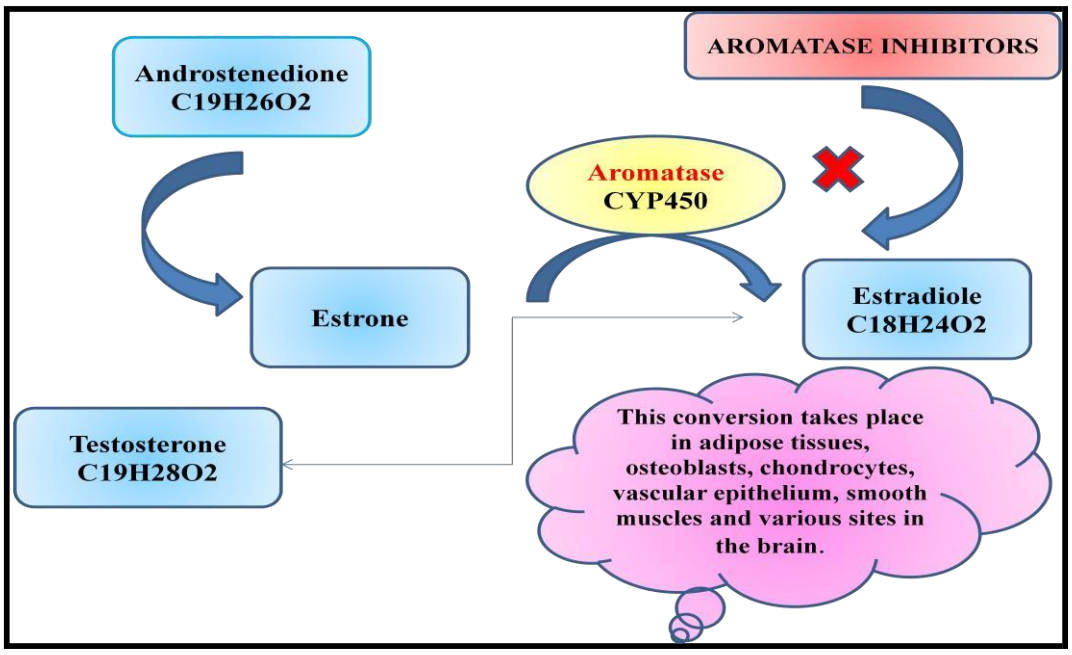

Figure 4: Mechanism of action of Aromatase Inhibitors.[30,32,35]

CLASSIFICATION OF DRUGS

Aromatase inhibitors categorized in the three main generations based on the reports of clinical trials.

Table 1: Classification of existing aromatase inhibitors [27,36,37,38]

GENERATION	STEROIDAL INHIBITORS TYPE I	NON STEROIDAL INHIBITORS TYPE II
FIRST	None	Aminoglutethimide
SECOND	Formestane	Fadrozole Rogletimide
THIRD	Exemestane (Aromasin)	Anastrozole (Armidex) Laterozole (Femara) Vorozole(Rivizor)

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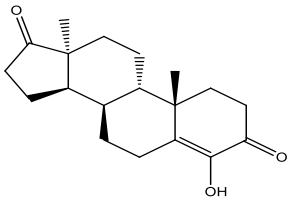
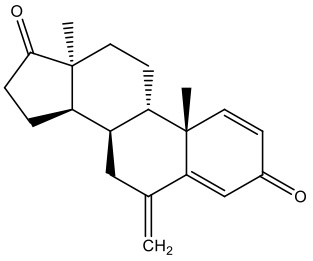
STRUCTURES OF POTENT AROMATASE INHIBITORS [36,37,38]

Type I Steroidal Inhibitors:

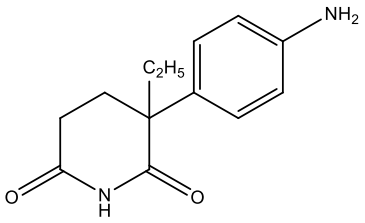


Formestane

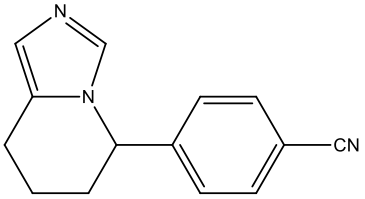


Exemestene

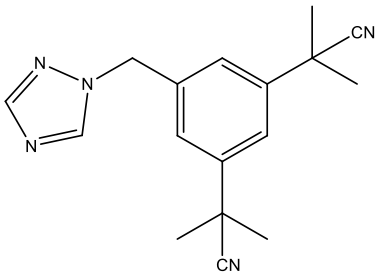
Type II Non Steroidal Inhibitors:



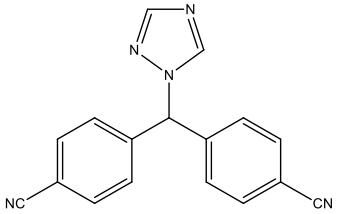
Aminoglutethimide



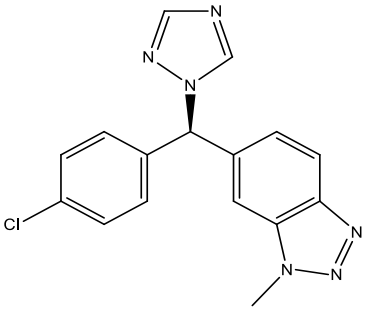
Fadrozole



Anastrozole



Latrolzole



varozole

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HORMONAL THERAPY USED TO TREAT BREAST CANCER COMBINATION WITH AROMATASE INHIBITORS

Estrogen is a hormone produced by the ovaries, responsible for the cause of many breast cancers. Women have hormone positive breast cancers for estrogen or progesterone receptors can be given hormone therapy to minimize the level of estrogen or to inhibit the effects of estrogen on the growth of cancer cells.

Tamoxifen and toremifene (Fareston) are therapeutic agents used to block estrogen from binding to breast cancer cells and are effective in both postmenopausal and premenopausal women. [39,40]

Several approaches are used to treat hormone-sensitive breast cancer:

- **Blocking ovarian function:** The ovaries are the main source of estrogen in premenopausal women, estrogen levels in postmenopausal women can be reduced by eliminating or suppressing ovarian function. This type of treatment that blocks or lowers estrogen level in ovaries is called ovarian ablation.
  Ovarian ablation can be done surgically to remove the ovaries (called oophorectomy) or by treatment with chemotherapy.

- **Blocking estrogen production:** Aromatase inhibitors are used to block/inhibit the action of an enzyme called aromatase, which used in the biosynthesis of estrogen in the ovaries and in other tissues. [39,40]

Hormone therapies used to treat hormone-sensitive breast cancer:

Adjuvant therapy for early-stage breast cancer: For adjuvant hormone treatment of premenopausal and postmenopausal women with ER-positive early-stage breast cancer, tamoxifen and the aromatase inhibitors anastrozole, letrozole, and exemestane are FDA approved drugs.

Treatment of advanced or metastatic breast cancer: Hormone therapy is also used to treat ER-positive breast cancer that has been reported in the breast, chest wall, or nearby lymph nodes after treatment (also called a locoregional recurrence). Two SERMs, tamoxifen and toremifene, are approved to treat metastatic breast cancer. [38,39,40]
Some women with advanced breast cancer are treated by a hormone therapy with the combination of cyclin-dependent kinase (CDK4 and CDK6) and Aromatase inhibitors.

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Table 2: Combination of CDK4 &CDK6 with AIs [42,43]

DRUG	COMBINATION	CANCER TYPE
Palbociclib (Ibrance)	Letrozole fulvestrant	HR-positive, HER2-negative metastatic breast cancer
Abemaciclib (Verzenio)	fulvestrant	HR-positive, HER2-negative metastatic breast cancer
Ribociclib (Kisqali)	fulvestrant	HR-positive, HER2-negative metastatic breast cancer
Alpelisib (Piqray)	fulvestrant	HR-positive, HER2-negative metastatic breast cancer

Neoadjuvant treatment of breast cancer: Hormone therapy is used to treat breast cancer to reduce tumor size before surgery (neoadjuvant therapy) has been studied in clinical trials. However, clinical trials exhibited that neoadjuvant hormone therapy with aromatase inhibitors could be effective in reducing the size of cyst/tumor in postmenopausal women, but it is not so far clear how effective it is in premenopausal women.

Sometimes the neoadjuvant treatment is used for HR-positive breast cancer when surgery demands to be delayed or who cannot tolerate chemotherapy.[41,42]

CONCLUSION

According to the clinical trial studies aromatase inhibitors are rapidly demonstrated as a beneficial addition to breast cancer therapy in postmenopausal women with estrogen receptor positive carcinoma. As results of ongoing clinical trials are available, it is acceptable that these agents will be used formerly in the course of the disease for the prevention of breast cancer and may be used successively to prolong hormonal therapy and delay the demand for chemotherapy.

Aromatase Inhibitors (AIs), such as letrozole, anastrozole, and exemestane, are the class of drugs that are used to treat both early and advanced stage hormone receptor positive breast cancer in postmenopausal women. They work by interfering with the body's ability to produce estrogen. AIs are not usually an effective treatment in women with functioning ovaries (including premenopausal women). Clinical trials have demonstrated a clear advantage to using either an AI instead of tamoxifen. In 2010, clinical guidelines were issued recommending that AIs be included in the treatment of postmenopausal women with hormone receptor positive breast cancer.

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