

## Review Article



## Role of Aromatase and Anastrozole in Cancer Treatment

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### ABSTRACT

Hormone medical aid is that the 1st targeted medical aid associate degreed additionally referred to as estrogen suppression therapy medical aid which regularly used as an adjuvant medical aid to cut back the chance of cancer back when surgery or cancer that has unfold. Aromatase inhibitors like anastrozole common type of the hormone therapy; it interferes with the body's capability to supply estrogen hormone from androgenic hormone by suppressing aromatase catalyst in post-menopausal girls with positive estrogen receptor breast cancer. This review is planned to assess the impact of anastrozole on aromatization mechanism in step with aromatase catalyst activity and estrogen level. Also as study the cytotoxic impact of anastrozole on three kinds of cell line breast cancer and survey the cell death mechanism for MCF-7.

**Keywords:** Estrogen, Breast cancer, Cryosurgery, Chemotherapy.

### INTRODUCTION

#### Breast Cancer Treatment

Breast cancer treatment choices vary depending on the cancer phase, its size, position, whether or not it's unfold to different locations in the human body and also the patient physical health.

Current treatments for breast cancer embody surgery, actinotherapy, chemotherapy, hormoning and targeted therapies<sup>1</sup>. These therapies could also be used alone or together betting on the stage of the malady<sup>2</sup>.

#### Surgical Medical Aid

Breast cancer surgery is been developed thoroughly over the past few years. With the appearance of breast-conserving medical aid (BCT), numerous ladies currently have the choice of conserving a cosmetically acceptable breast while not sacrificing survival<sup>3</sup>.

Generally, breast protective therapy is outlined as removal of the primary breast tumor with a rim of adjacent traditional breast tissue adequate to reach negative surgical procedure margins, with or without axillary sentinel node (SN) biopsy or dissection, followed by irradiation<sup>4</sup>.

#### Minimally Invasive Procedures

These minimally invasive techniques embody endoscopic lumpectomy, vacuum-assisted connective tissue excisional biopsy, and connective tissue thermo ablation with radiofrequency, cryotherapy or laser.

Minimally invasive techniques are at the forefront of surgical and interventional innovation and are being assessed within the setting of clinical trials, as they are

doing not represent current customary of take care of breast tumors, benign or malignant<sup>5</sup>.

#### Radiofrequency Ablation

Radiofrequency ablation (RFA) is one in every of the foremost established varieties of native treatment in patients with tumors, that tumors square measure destroyed in place by thermal activity and super molecule denaturation<sup>6</sup>. High frequency (460 kHz) AC flows from UN insulated conductor tips into close tissue. Because the tissue ions commit to follow the amendment in direction of the AC, ionic agitation leads to frictional heating. The tissue close the conductor, instead of the conductor itself, is that the primary supply of heat<sup>7</sup>. Though there many potential mechanisms for cellular injury because of radiofrequency energy, the predominant mechanism is probably like thermal injury due to the radiofrequency-induced heating of tissue<sup>8</sup>.

#### Cryotherapy

Cryosurgery, that it's additionally referred to as cryotherapy or cryoablation, is used sometime to treat early-stage cancer by phase transition (freezing) it. Most doctors don't use cryosurgery option as first treatment for cancer, however it's generally associate degree possibility if cancer has came back when different treatments had been used earlier.

Between 1999 and 2007, cryotherapy was dispensed on fifty three cases with biopsy-proven breast cancer with age vary 38-81 years<sup>9</sup>, but it ought never to be use to treat lesions of unsure designation<sup>10</sup>.



## Radiotherapy After Surgery

Radiotherapy (RT) is one in every of the first treatment choices in cancer management, effectively saving and prolonging lives. RT is widely known as one of the safest areas of recent medicine; but, however, when errors occur, the consequences for the patient can be major<sup>11</sup>. Radiotherapy uses high energy x-rays to destroy cancer cells. A number of the normal cells is probably also can be effected (damaged), however they're higher at repairing themselves than cancer cells. It could also be given before or after surgery treatment. It (radiotherapy) will facilitate to kill any of cancer cells which may be left behind when it's used after the surgical option. In bound cases, chemotherapy is given along with radiotherapy<sup>12</sup>.

## Adjuvant Chemotherapy

Chemotherapy works by stopping or speed control for the expansion of cancer cells that grow and divide quickly. However it may destruct healthy cells that divide quickly, like those who line your mouth and intestines or cause your hair to grow. Damaging healthy cells might cause some other side effects<sup>13</sup>. Adjuvant chemotherapy results decreasing of breast return incidence in scrutiny with conservative surgery and RT alone. Early adjuvant systematic chemotherapy in patients at substantial risk of metastases is believed to be vital<sup>14-15</sup>.

## Endocrine Therapy

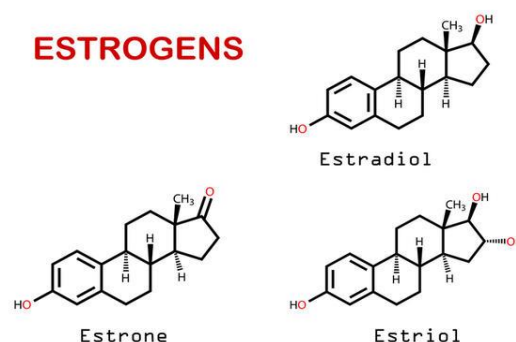
Endocrine therapies, additionally referred to as hormonal therapy, for breast cancer are used for over a century<sup>16</sup>. The scenario that changes the hormonal balance of the patient with breast cancer may lead to alter in tumor growth and regression of pathological process malady and its might acknowledged even before hormones and endocrine agents were available<sup>17</sup>.

The history of endocrine medical aid for superior breast cancer began with the seminal discovery by St. George Beatson (1896) that female internal reproductive organ ablation might cause tumor regression in biological women. Female internal reproductive organ estrogen synthesis ceases at the change of life, postmenopausal female still have plasma estrogen hormone levels present at low concentration. Previously, it was believed to occur by adrenal organ synthesis, and later it became clear that the adrenals are contributors of circulating androgens, which it's converted later into estrogens in several body compartments<sup>18</sup>.

The mechanisms of endocrine therapies action are in three folds: they will lower the estrogen hormone level within the tumor (ophorectomy, aromatase inhibitors), they will adjust estrogen receptors (SERMS [tamoxifen, toremifene]); or they will adjust the estrogen receptor (ER) with uncontaminated antagonist activity, e.g., ER down-regulator (fulvestrant). However, high estrogens dose, progestin, and androgens have activity against ER+ tumors. The precise action mechanism remains unclear<sup>19</sup>.

Estrogens are naturally occurring steroid hormone that functions as the primary feminine hormone.

Generally there are measure three categories of estrogen: estrone (E1), estradiol (E2), and estriol (E3) as shown in Figure (1). Estrogens are created primarily by the ovaries; some also are created in smaller amounts by different tissues like the liver, adrenal glands, and also the breasts (Figure 1). These secondary sources of estrogens are particularly vital in postmenopausal women<sup>20</sup>; as a result of it'll be the supply of estrogen hormones once the ovaries stop to supply estrogen<sup>21</sup>.



**Figure 1:** classes of estrogen<sup>21</sup>.

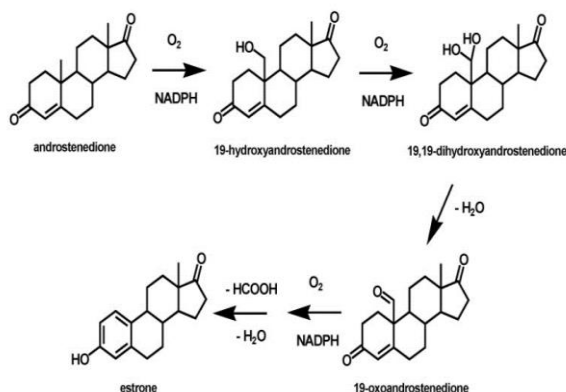
All three kinds of estrogen hormone be created from androgens (androstenedione or testosterone), this adaptation (aromatization) is catalyzed by aromatase catalyst<sup>22</sup>.

## Aromatase Enzyme

Aromatase (cytochrome P450), additionally named as estrogen synthesizer, is an enzyme chargeable for a key step in the synthesis of estrogens. Aromatase is a 503-amino acid super molecule encoded by the CYP19 gene that is located at 15q21.2 in humans and contains 10 exons<sup>23</sup>. It's expressed in many tissues, together with body covering fat, liver, muscle, brain, ordinary breast tissues, and mammary adenocarcinoma (the predominant source of estrogen in postmenopausal women)<sup>24</sup>. It catalyzes the last steps of estrogen hormone synthesis from androgens specifically transforms androstenedione to estrone (E1) and androgenic hormone to estradiol (E2) (the predominant supply of estrogen hormone in postmenopausal women). This conversion contains three successive oxidation reaction steps, every one required one mole of O<sub>2</sub> and nicotinamide adenine dinucleotide phosphate (NADPH). In the first step, the androgen is hydroxylated at C-19 to afford the 19 - hydroxy intermediate<sup>25</sup>.

The reaction happens with the configuration retention that is characterized by a major normal kinetic atom impact. Within the second step 19-hydroxy steroid undergoes second hydroxylation round of C-19 to allow gem diolic cluster as presented in Figure (2). This on subsequent dehydration results, in the corresponding aldehyde, whereas there's enough proof to clarify the first and also the second steps, the supposed oxidation

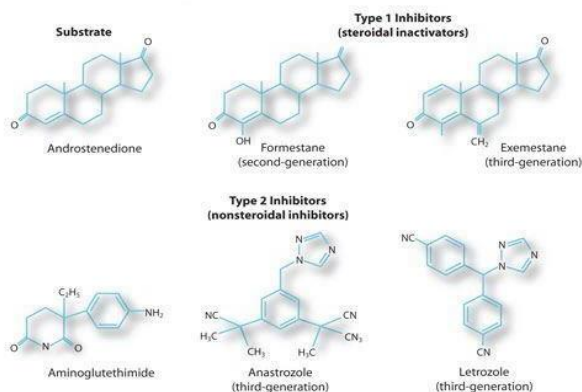
bond cleavage between C<sub>10</sub> and C<sub>19</sub> to afford estrogen hormone and formic acid within the third<sup>26</sup>. Blockade of any conversion within the pathway probably reduce or ends up in estrogen production. However additional specific suppression can result from inhibition of the ultimate step that's distinctive to estrogen biosynthesis<sup>27</sup>.



**Figure 2:** Mechanism of Estrogen Production<sup>27</sup>.

The aromatase catalyst has four- to a five folds higher affinity for androstenedione compared with testosterone<sup>28</sup>. Thus, aromatization of androstenedione into E1 is that the major pathway of estrogen synthesis in postmenopausal women. In other hand, E1 is inactive by itself with relation to stimulating estrogen hormone receptor activation, which it's simply moved to form E2 by multiple dehydrogenises<sup>29</sup>.

### Aromatase Inhibition (AIs)



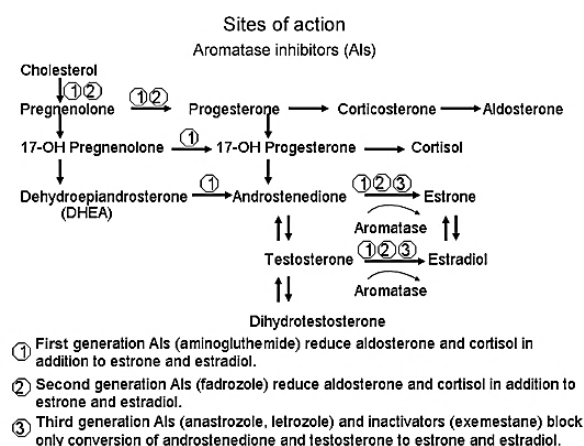
**Figure 3:** Chemical structures of aromatase inhibitors<sup>32</sup>.

Aromatase inhibitors have a central role in endocrine therapy for estrogen receptor (ER)-positive breast cancer in postmenopausal women<sup>30</sup>. It obstructs with the body's readiness to supply estrogen hormone from androgens by suppressing aromatase enzyme activity. Aromatase inhibitors use two diverse mechanisms to prevent the action of aromatase and thereby slow or cut back production of the estrogen. Kind I inhibitors, like exemestane and formestane, are androgen-like compounds that bind irreversibly to the substrate-complex, inflicting permanent enzyme inactivation<sup>31</sup>. This might probably cause prolonged estrogen hormone deprivation even when the drug is cleared. These drugs

also are called aromatase inactivators. Kind II inhibitors, like aminoglutethimide, letrozole, and anastrozole, are nonsteroidal complexes that reversibly bind to the heme-iron element of the aromatase enzyme, thus inhibiting the conversion of androgenic hormone to estrogen hormone in an indirect fashion<sup>32</sup>. Figure 3 displays the chemical structures for each kind.

Basically, three generations of AIs are developed as Winer 2005 was claimed<sup>33</sup>. Every successive generation has been related to higher specificity for the aromatase enzyme as shown in Figure 4, fewer adverse events, and greater control of aromatase activity.

The utilities of first and second generation of AIs were restricted by undesirable events, such a rashes, fatigue, dizziness, ataxia, nausea and disgorgement, also as by a decrease of enzyme selectivity. Third generation AIs is a superior to earlier versions as a result of their related to less adverse events and larger suppression of aromatase activity (see Figure 4).



**Figure 4:** Metabolic pathways differentially targeted by aromatase inhibitors (AIs)<sup>34</sup>.

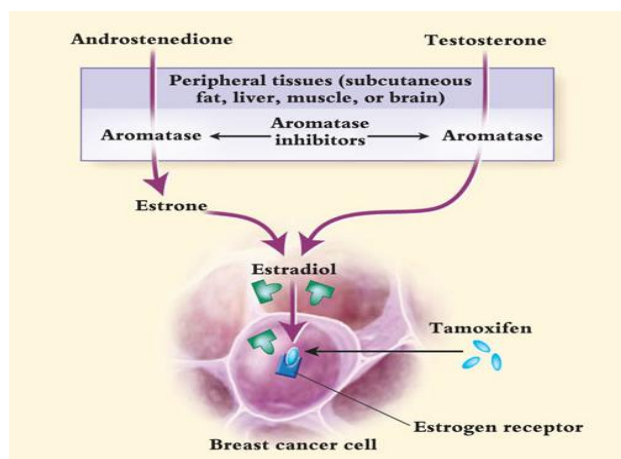
The aromatase inhibitors are highly specific and selective for the aromatase enzyme and are well tolerated by the patients. One in every of the causes, why aromatase inhibitors are effective second-line therapies, is that their action mechanism varies from estrogen antagonist (Figure 5). Tamoxifen (Estrogen antagonist) blocks the action of estrogen at the receptor stage, while aromatase inhibitors block estrogen synthesizing in tissues marginal including the breast.

However, estrogen antagonist may be a partial estrogen hormone agonist in the breast, which can seems in but best anticancer activity.

Anastrozole, letrozole, and exemestane are showed to be effective first line treatment choices after surgery for patients with hormone-dependent advanced breast cancer. In two separate trials, anastrozole had shown to be either equivalent or superior to the estrogen tamoxifen<sup>35-36</sup>.

Despite the deep interest of aromatase as a drug target as anti breast cancer detailed structural and spectroscopical information on this enzyme became accessible only during the past few years.

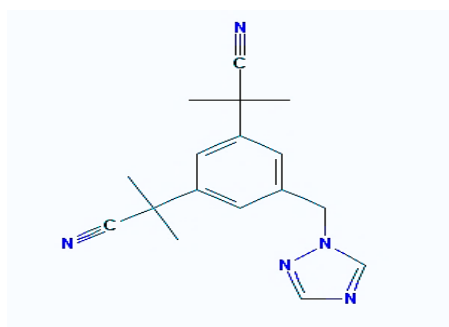
As such, the enigmatic mechanism of the ultimate aromatization step remains a matter of dialogue<sup>37</sup>.



**Figure 5:** Comparison between aromatase inhibitors and tamoxifen<sup>34</sup>.

### Anastrozole

Chemically referred to as 2,2'-(5-((1H-1, 2,4-triazol-1-yl)methyl)-1,3-phenylene)bis(2-methylpropanenitrile), is a non-estroidal, third-generation and extremely potent aromatase-inhibiting drug approved for treatment of breast cancer after surgery, also as for metastasis in post-menopausal women (see Figure 6)<sup>38</sup>.



**Figure 6:** Anastrozole Structure<sup>38</sup>.

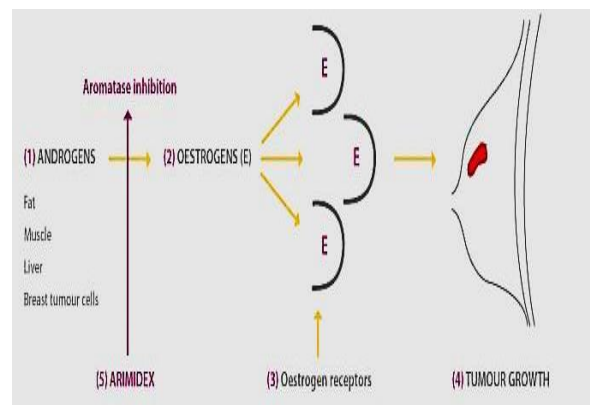
**Table 1:** Degree of Whole-body Aromatase Inhibition by Drugs Used in Breast Cancer Clinical Efficacy<sup>43</sup>.

Drug	Dose	Mean Percentage Inhibition	Reference
Aminoglutethimide (+ hydrocortisone)	1000 mg (+ 40 mg)d	90.6	MacNeill
Formestane	250 mg/2 w (im)	84.8	Jones
Fadrozole	2 mg/d	82.4	Lonning
Vorozole	1 mg/d	93.0	Van der Wall
Letrozole	2.5 mg/d	> 99.1	Geisler
Anastrozole	1 mg/d	97.3	Geisler
Exemestane	25 mg/d	97.9	Geisler

It is given orally, is well tolerated, and provides nearly complete estrogen hormone suppression both systemically and intratumorally, as in Figure 7<sup>39</sup>.

Anastrozole is effective in treating advanced breast cancer and at a dose of one mg once-daily; it considerably will increase survival time compared with megestrol acetate<sup>40</sup>. Moreover, anastrozole has shown its impact in reduction of breast cancer return rate.

This trial led to the endorsement of anastrozole by the U.S. Food and Drug Administration for adjuvant treatment of endocrine receptor-positive early stage breast cancer<sup>41</sup>.



**Figure 7:** Mechanism Action of Anastrozole<sup>40</sup>.

Table 1 displays comparison study for the aromatase inhibition degree achieved among drugs of latest importance.

It bestowed data promotes that aminoglutethimide and also the second inhibitors generation suppress aromatase by very little over 90% at their clinically used dosages<sup>42</sup>, whereas the new third-generation compounds approach absolute ablation of aromatase activity.

Anastrozole was found to inhibit by larger than 97% in all told examined patients<sup>43</sup>.



## CONCLUSION

Anastrozole was possessing cytotoxic impact against breast cancer cells (MCF-7), liver hepatocellular cancer cells (HepG2) and glandular cancer cells (PC-3), determined *in-vitro* by MTT assay.

Anastrozole has two effects on breast cancer, inhibition of aromatase enzyme that causes inhibit aromatization mechanism and toxic impact.

However, Aromatase activity in postmenopausal breast cancer patient treated with anastrozole is depending on the period of treatment.

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