Review Article

Aromatase Inhibitors: Development and Current Perspectives

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ABSTRACT

Aim: Breast cancer is one of the most common cancers among women, consistently elevated estrogen level in the blood associated with persistently in breast cancer found in many studies. The mechanisms of carcinogenesis whereby cancer is associated involved in the conversion of androgen to estrogen in the presence of enzyme aromatase. **Materials and Methods:** Aromatase is a (CYP19), a cytochrome P450, which is the enzyme that synthesizes estrogen. Aromatase which is expressed in higher concentration in breast play a pivotal role in the origin and progression of breast cancer. *In situ* inhibition of aromatase enzyme accomplished by the prevention of aromatase expression in breast cancer. **Results:** The success of aromatase inhibition could result in the suppression and progression of breast cancer. One of the ways to reduce the incidence of breast cancer by inhibiting estrogen biosynthesis in breast tissue. Aromatase inhibitor therapy is considered for second-line treatment in patients who fail anti-estrogen therapy. **Conclusion:** Several potent and selective aromatase inhibitors have been developed and used to treat breast cancer. Some of them have passed clinical trial phase II. Development in the field has encouraged us to review work on the Aromatase inhibitor.

Key words: Non-Steroidal aromatase inhibitor, Aromatase, Cancer, Aromatase Inhibitors.

INTRODUCTION

According to WHO women breast cancer is the most recurring cancer, hit almost 2.1 million women each year, and also the greatest root for cancer-related death. In 2018 it was estimated that 15% of all cancer death in women due to breast cancer which is approximately 627,000 women died from breast cancer. Familial and hereditary risk factors contribute to the occurrence of breast cancer. Other factors that increase risk in breast cancer are mutation in BRCA1, BRCA2, and p53genes.[1] Patients with familial or non-familial gynecomastia Elevated expression of aromatase reported in breast epithelium, skin fibroblast, and peripheral lymphocytes.[2,3] Aromatase is an enzyme involved in the production of estrogen from the androgen and is responsible for catalyzing the last rate limiting/crucial/ key step for the biosynthesis of estrogen.[4] These are a group of steroid hormones that promote the development and maintenance of female characteristics of the body.[5] Estrogen signalling pathways take part in diverse particularly cell survival and proliferation. In addition to the reproductive system, estrogen play important role in the cardiovascular system, musculoskeletal system and brain,[6] Non-steroidal aromatase inhibitor (aminoglutethimide) act by binding with the heme moiety (non-covalently and reversible) of the enzyme aromatase and prevent the binding of androgens. It was hypothesized that this may involve the interaction of the nitrogen atom of aminoglutethimide with the heme moiety.[7] The research was carried out and some imidazole antimycotic drugs were found to be effective in inhibiting aromatase but were not suitable for antitumor activity in breast cancer. Miconazole, clotrimazole, ketoconazole was found to have better inhibitory activity then aminoglutethimide

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but are not used for antitumor activity. Azole derivatives like vorozole anastrozole and fadrazole all having 1,2,4-triazole ring were found to have excellent antitumor activity in the treatment of breast cancer by inhibiting aromatase enzyme.[8-10]

Why aromatase inhibitors?

Aromatase reaction is the last step in the biosynthetic pathway of estrogen. The inhibition of this last step ensures that the bio-synthesis of other steroids classes remains unaffected.[11]

Aromatase inhibitor's role in post-menopausal: Primary estrogen source in post menopaused women is aromatase activity in breast, bone, vascular endothecium, and CNS. Also, gonadotropin regulation cannot regulate the aromatase level in post menopaused women and this avoids the complications which are due to feedback regulatory mechanism that increases LH and FSH after aromatase inhibition. Therefore, AI'S are employed for the therapy of breast cancer in post-menopause women as shown in Figure 1.[12-14]

Biosynthesis

Steroids producing cells are characterized by intracellular deposits. They contain mitochondria containing cholesterol side-chain enzyme (P450 SCC) and Esterified cholesterol. They also contain aromatase enzyme 3, 8 hydroxysteroid dehydrogenase (HSD) / isomerase 17,18-HSD enzymes, these enzymes are present in the smooth endoplasmic reticulum and Golgi bodies, involved in the formation of P storage granules.[15,16] The amount of smooth endoplasmic reticulum, mitochondria, Golgi bodies, and lipid in the granulosa cells are less in the smallest growing follicles.

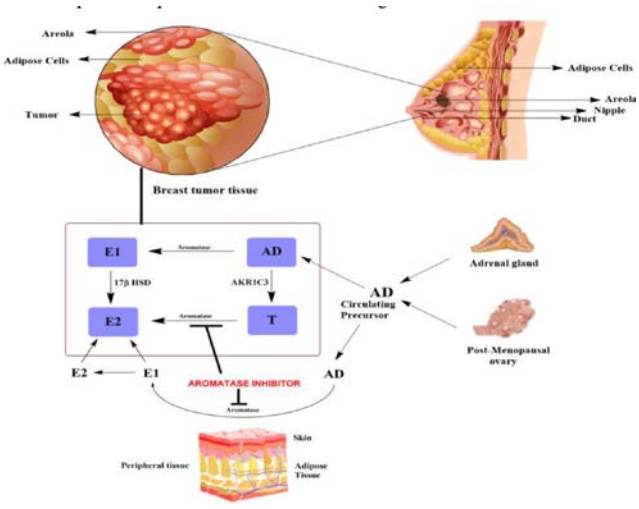

Figure 1: Regulation and its Expression of aromatase in the breast cancer and peripheral system.

A drastic change is seen in developing granulosa cells. This suggests that developing follicles increase the rate of Steroidogenesis. Steroidogenesis, stimulation of follicular growth, and steroidogenic enzyme mRNA are promoted by FSH and LH.[17] This leads to promotion in the growth of steroidogenic cells. Aromatase or estrogen synthase is an enzyme responsible for a key step in the biosynthesis of estrogen.[18-20] The gene that encodes an aromatic protein in humans is CYP19A1 and rangers approximately 123kb on chromosome 15q21.2. It consists of 93 Kb 5'-unsaturated region (UTR), 30kb coding region, and 3' end. The coding region starts with ATG, translation start site on Exon II as the coding region contains 9 exons (II-X) coding region.[21] Several unsaturated first exons are regulated by the tissue-specific promoter in 5'-UTR. There is 10 alternate tissue-specific promoter found in humans which includes I.1, I.2, I.2a in the placenta, I.4 in adipose tissue and skin, I.5 in fetal tissue in the brain, I.7 in bones, I.3 in adipose tissue PII in gonads and adipose tissue.[22,23] These promoters regulate aromatase expression in different tissues.[22,24] Cytochrome P450 is a superfamily of enzymes that catalyzes the estrogen biosynthesis.[25] The phenolic ring a characteristic feature of estrogen formed by binding of C19 steroid substrate and catalyzes the series of reactions with the help of heme protein. P450 is a flavoprotein, NADPH cytochrome P450 reductase.[26] These are ubiquitous proteins in the endoplasmic reticulum. When it comes in contact with NADPH it transfers reducing equivalents to any form of cytochrome P450. The reductase may be the product of a single gene. In superfamily of genes cytochrome P450, the aroma is the only member of gene family 19 denoted as CYP19. It is denoted as CYP19 based on the fact that oxygen attacks on the angular methyl group at C19. For the metabolism of C19, the aromatase reaction utilizes three molecules of NADPH and three molecules of oxygen. Various shreds of evidence suggest that all three oxygen molecules are used in the oxidation of the C19 angular methyl group which forms formic acid. This process occurs simultaneously with the aromatization of a ring to phenolics structures. This ring is characteristic of estrogen as illustrated in Figure 2.[25,27,28]

Structure

At the junction of beta-sheet 3, B-C loop, and the I and F helices the catalytic site of the aromatase enzyme is located. The C19 is placed in proximity to 4.0 Å of an iron atom and beta face of Androstenedione towards Fe group of the enzyme. Binding pocket is formed of about 400 Å by moving I helix Backbone by 3.5 Å. Residue P308 plays an important role in the Catalytic activity of

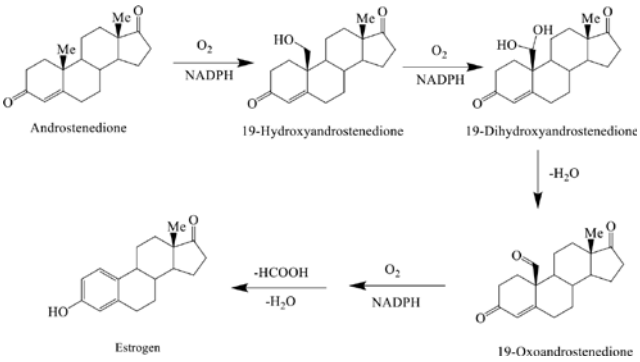

Figure 2: Mechanism Cascade in the biosynthesis of Aromatase Enzyme.

aromatase as without P308 steric hindrance can decrease catalytic activity.[27] This P308 located on the distal side of I helix from androstenedione. It is not present in any of Cytochrome P450 family enzymes and can be used for site-directed mutagenesis studies.[29] Several hydrophobic Residues are pilled against the alpha face Backbone. This long chain results in a deep spherical active site which increases specificity. Long-distance of steroids makes them more specific against aromatase.[6,30,31] The active site of aromatase is present in the spherical molecule illustrated in Figure 3 at the centre of the heme distal cavity. Various studies showed that androstenedione binds with C19 at 4.0 Å from the Fe atom and β face towards the heme group.[27] Various polypeptide segments present in the catalytic cleft of different loops and helix are Ile305, ASP309, Thr310, Ala306 from I helix. Trp224 and Phe221 from F-helix, Phe134 and Ile133 from B-C loop, Val370, Val373, Leu372 from K-β3 loop, Leu477 and Ser478 from β8-β9 loop and Met 374 from β3. The cavity of complementary to androstenedione's shape is formed by tight packing against the steroid backbone of hydrophobic residue and porphyrin ring of heme.[32] As shown in Figure 3 a and b different combinations of side-chain residue make interaction and attachment on androstenedione.[33-35] Vander wall forces approaching substrate from the alpha face and fallows contour, some make contact at the edges. All these residue and polypeptide forms a pocket of approx. 400 Å with tightly encloses androstadienone. The presence of two hydrogen bonds and their geometrics are arranged in such a way that 3-Keto O1 and a water Oxygen atom are in the carboxylate plane, this provides strong hydrogen bonding interaction. In ASP 309 sidechain protonation and deprotonation are required of the carboxylate group for substrate binding interaction and catalysis. This acts as a proton relay network which helps in androgen to estrogen conversion in which water molecule and polar

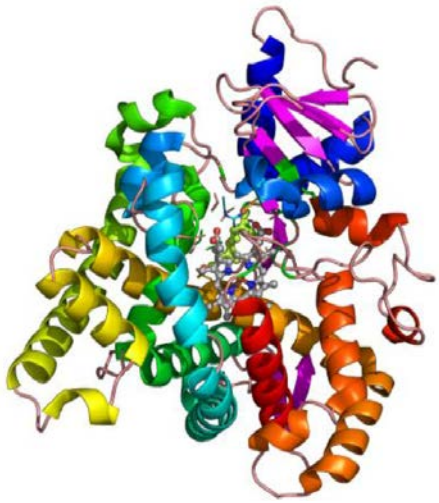

Figure 3: Ribbon diagram showing the structure of the human placental aromatase with ligand androstenedione.[30]

side chain act as a proton source. The only hole in the binding pocket is located where 3 water molecules are present. This channel opens in the exterior part of the protein surface. The flexibility of tertiary structure allows smooth passage of steroidal structure.[36,37]

Generation

First Generation

Aminoglutethimide

Aminoglutethimide is manufactured by Novartis and marketed under the name of Cytadren, for anticonvulsant activity in 1966 and discontinued because it has more effects on the adrenal gland. It was approved by the FDA on 10/29/1980 for the treatment of breast cancer and other hormone-sensitive cancers in 1980.[38] It was discontinued later, its chemical name is 3-(4-aminophenyl)-3-ethyl-2,6- piperidinedione. The drug inhibits the conversion of cholesterol to Δ5 -pregnenolone leads to a decrease in the production of adrenal glucocorticoids, mineralocorticoids, estrogens, and androgens. Simultaneous administration of hydrocortisone is necessary to suppress the increased levels of ACTH. Cytadren is administered orally of 250 mg tablets. Use of aminoglutethimide (1000mg conventional dose) shows early side effects which are mild and frequent, while late side effects are infrequent. About 40% of the patients develop lethargy and ataxia (usually disappear over 4 weeks). About one-third of the patients show a morbilliform skin rash along with fever. It is moderate and rarely serious (erythroderma syndrome). Other side effects occur infrequently but are clinically relevant, such as hypothyroidism, hematologic toxicity (prolonged thrombocytopenia, agranulocytosis, pancytopenia), pulmonary haemorrhage

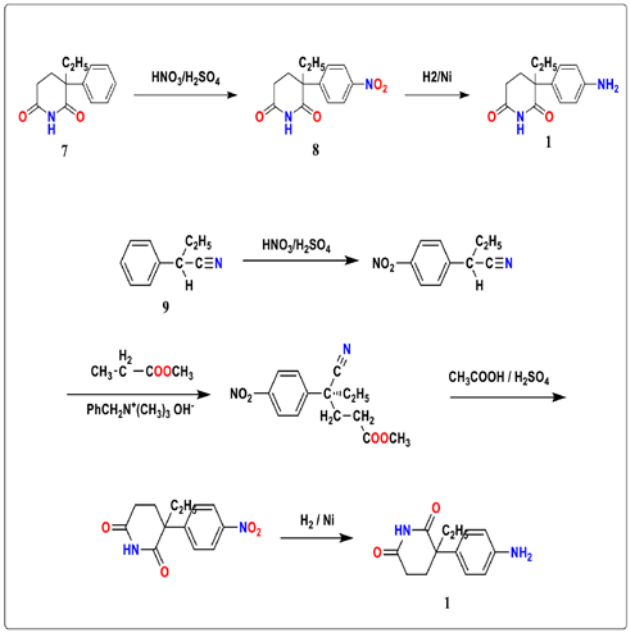

Figure 4: Synthesis of Aminogluthemide.

due to alveolar damage, cholestasis, and systemic lupus erythematosus.[39,40] Synthesis of 1 (Figure 4) requires commercially available Glutethimide 7 which is nitrated to form 2-(4-nitrophenyl)-2-ethylglutarimide 8 reductions of the nitro group using nickel catalyst to give aminoglutethimide 1. As gluthemide is expensive another method for synthesis is using commercially available 2-phenylbutyronitrile. 2-phenylbutyronitrile 9 is nitrated to form2-(4-nitrophenyl)butyronitrile under Michael addition reaction conditions in the presence of benzyl trimethyl, ammonia hydroxide is added to methyl acrylate, the product obtained undergo acid hydrolyses using a mixture of acetic acid and sulphuric acid, a cyclization occurs to 2-(4-nitrophenyl)-2-ethylglutarimide, the product is reduced by hydrogen to give the desired product aminoglutethimide 1.[41,42]

Testololactone

The first steroid used for breast cancer treatment is Testolactone. Testolactone is manufactured by Bristol-Myers Squib and marketed under the name of Teslac, which was approved by the FDA in 1970. It is a synthetic antineoplastic agent with a six-membered lactone ring in place of the usual five-membered carbocyclic D-ring of androgen steroid nucleus.[43] Testolactone is chemically designated as 13- hydroxy-3-oxo-13,17-secoandrosta-1,4-dien-17-oic acid δ-lactone. It is available in the form of tablets 50mg for oral administration, an increase in a dose up to 1000mg leads to increase renal tubular reabsorption of calcium but no serum calcium concentration observed. Now it is discontinued by the FDA. Exact mechanism of antineoplastic activity of Testolactone has not been established. The principal mechanism is suggested to be a reduction in estrone synthesis from adrenal androstenedione by inhibiting the aromatase enzyme.[42,44] Although it is having some similarities with testosterone but not having any androgenic effects. The drug shows non-competitive, irreversible inhibition. This inhibition leads to suppression of tumour growth. Testololactone demonstrated a very low rate of toxic effects, consisting of vomiting, nausea, and diarrhoea, with no side effects of an endocrine nature. The synthetic approach involved the initial formation of the lactone ring of ring D by Baeyer-Villiger Oxidation using peracetic acid followed the formation of the intermediate by addition of double bond in ring A by using selenium dioxide oxidation.[39,45,46]

Second Generation

Formestane

Formestane was marketed under the name of Lentrone by Ciba-Geigy Pharmaceuticals was not approved by FDA.[47,48] intramuscular injection form Lentrone was approved in Europe has been withdrawn. Formestane was the first selective, second-generation, type I, steroidal aromatase inhibitor used in the treatment of estrogen-receptor-positive breast cancer in postmenopausal women. Formestane suppresses estrogen production from anabolic steroids or prohormones.[49] Its chemical name is 4-Hydroxyandrost-4-ene-3,17-dione. Major systemic side effects include hot flushes and vaginal spotting, lethargy, rash, nausea, and dizziness.[50] Formestane (3) in Figure 5 was synthesized from testosterone (9). The oxidation of testosterone (9) with Jones reagent gives androst-4-ene-3,17-dione which on

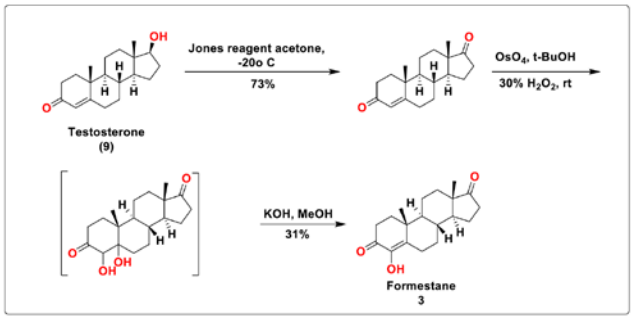

Figure 5: Synthesis of Formestane.

Hydroxylation with oso4/H2O2 followed by alkaline dehydration of the resultant diols gave formestane (3).[51]

Third Generation

Exemestane

Exemestane (Aromasin) (Pfizer) is a US FDA approved drug in 1999 it is a steroid aromatase inhibitor chemically

known as 6-methylideneandrosta-1,4-diene-3,17-dione (IUPAC name (1S,2R,10R,11S,15S)-2,15-dimethyl-8-methylidenetetracyclo[8.7.0.02,7.011,15]heptadeca-3,6-diene-5,14-dione) used as a adjoint therapy in postmenopausal women for advanced breast cancer which is estrogen receptor-positive. It is also used in advance best cancer who received tamoxifen for about two to three years and then switch to exemestane to complete 5 years of therapy. A single 25 mg dose of Aromasin was found to be effective in both types of cancer it shows a long effect in reducing estrogen synthesis. Exemestane is a steroidal aromatase inhibitor that binds irreversibly to the aromatase enzyme. The structure of androstenedione which is natural substrate and exemestane have similarities which show fake substrate binding to the aromatase enzyme. This long-duration action can be due to irreversible reaction on aromatase inhibitor as compared to the pharmacokinetic properties of the drug. Adverse drug reaction scene in early breast cancer for hot flashes, arthralgia, fatigue, increased sweating and headache and in advanced breast cancer, it was observed that hot flashes, fatigue, increased sweating were common additionally increase in appetite was seen. Exemestane (4) in Figure 6 is synthesized in various steps. First, a vilsmeier-Haack reagent is synthesized for which paraformaldehyde and dimethylamine hydrochloride in isopentanol was refluxed using dean- stark separator. Subsequently addition of androsta-1,4-dien-17 β –ol-3-one (10) in the mixture after cooling to 10 to 15°C and then refluxed for 15 hr which give 6-methylene derivative (11). Further Jones oxidation in acetone and

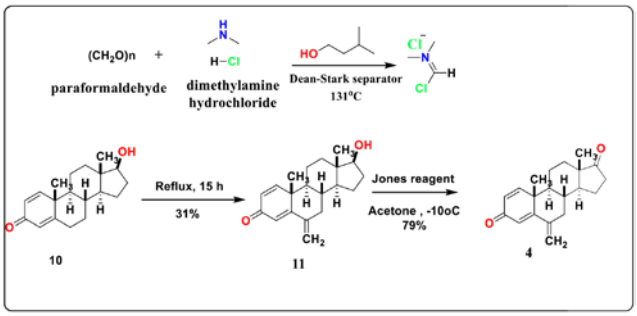

Figure 6: Synthesis of Exemestane.

recrystallization by ethanol and water (65:35) yields exemestane (4).

Fourth Generation

Anastrozole

Anastrozole (Arimidex ® Astra Zeneca) is a US FDA approved in 1995 fourth-generation non-steroidal aromatase inhibitor indicated for postmenopausal women with early hormone receptor-positive breast cancer, locally advanced or metastatic and in advanced breast cancer if the disease is progressed after initial tamoxifen therapy.[52,53] Chemically it is nonsteroidal benziltriazole derivative. IUPAC name 2,2-[5-(1H-1,2,4-triazol-1 ymethyl)-1,3-phenylene]bis(2-methyl-propiono-nitrile)). It is an orally active drug prescribed 1 mg tablet once daily. It acts by inhibiting aromatase enzyme by binding reversibly to heme ion of CYP450 which reduces biosynthesis of estrogen. The adverse reaction seen in early breast cancer is hot flashes, asthenia, arthralgia, hypertension, nausea and vomiting, and arthritis. In the latest finding embryo-fetal toxicity is seen in animal studies and clinical trials in pregnant women.[54-56] Displacement of bromine in 3, 5 bis (bromomethyl) toluene (12) with nitrile group by SN2 mechanism forms 3, 5 bis nitrile toluene (13) in presence of potassium nitrate, Tetra butyl ammonium bromide and phase transfer catalyst. The bis nitrile product formed in DMF in excess of methyl iodide was deprotonated with the help of sodium hydride gives bis dimethylated product (14). This bis dimethyl product undergoes Wohl Ziegler reaction in the presence of benzoyl peroxide and n-bromosuccinimide. Finally,

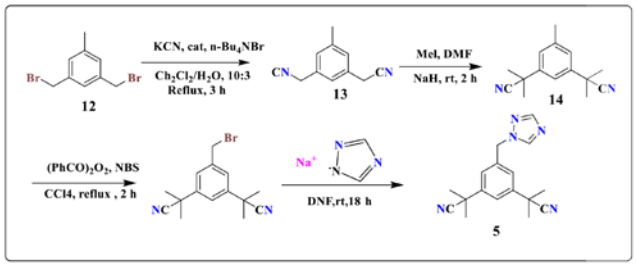

Figure 7: Synthesis of Anastrozole.

anastrozole as illustrated in Figure 7 is formed by the replacement of benzyl bromide with sodium triazole by an SN2 mechanism.[57]

Letrozole

Letrozole (Femara® Novartis) a US FDA 1997 and EU 1996 approved is a non-steroidal aromatase inhibitor prescribed for advanced breast cancer and as adjuvant therapy in postmenopausal women.[58,59] Chemically it is 4,40-[(1H-1,2,4-triazol-1-yl) methylene] bis-benzonitrile as shown in Figure 8. In the structure cyanobenzene moiety acts similarly as a steroidal backbone in non-steroidal aromatase inhibitor, this led to competitive inhibition.[60] The dose recommended is 2.5 mg tablet once a day. The duration of treatment is not confirmed but

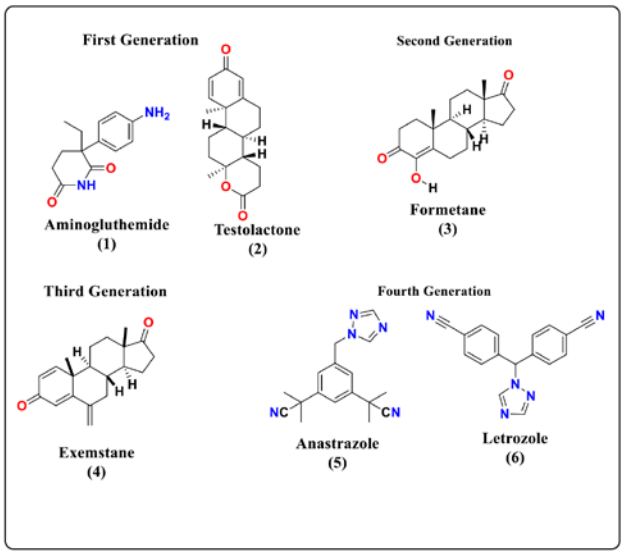

Figure 8: Generation of Aromatase Inhibitors.

should be continued until tumour growth is reduced.[61] Letrozole is a competitive inhibitor of the aromatase enzyme. It acts by binding to heme ion of cytochrome P450 and reduces the level of estrogen, estradiol in serum. Arthralgia and arthritis were the major side effect of letrozole.[62] Other side effects were osteoporosis and hypercholesterolemia. The synthesis starts with SN2 substitution with imidazole in 4- bromomethyl-benzonitrile as a starting material in the presence of methylene chloride. Subsequent deprotonation of the adduct in the presence of DMF, potassium- t- butoxide, and para flurobenzonitrile forms letrozole. This snar reaction forms as oil. Oil is converted into crystal form by converting into hemisuccinate. Its melting point is 149 to 150°C.[57,63]

Resistance

Aromatase inhibitors function by blocking the aromatase enzyme so that less estrogen (endogenous) is available to stimulate the growth and proliferation of ER+ breast cancer cells.[64] The use of AI also reduces the risk of recurrence. Therapeutic resistance is common with AI and is responsible for limiting the use of AI for endocrine therapy.[65,66] In the treatment with AI if the therapy is not enough effective to decrease the size of the tumour and there is inadequate growth inhibition by AI is recognized as clinical resistance to AI.[67] In contrast to this, molecular and pathological changes are seen in the clinically resistant tumour by AI treatment.[65,68] Two types of resistance are known and recognized clinically while treating with endocrine therapy. Primary resistance (*denovo resistance)*, ER+ tumours that are inadequate to respond to the endocrine treatment or the ER+ tumour is not sufficiently responding to endocrine manipulations is recognized as primary resistance to AI. Secondary resistance (*acquired resistance),* ER+ tumour showing response to the therapy initially but later becomes resistant towards the therapy. Acquired resistance suggests that, while giving treatment with AI inductive changes or clonal selection occurs that changes the effectiveness of therapy and resulting in resistant cellular phenotype. Primary and secondary types of resistance might have common mechanisms of resistance.[69,70] Cross-resistance and non-cross resistance. Total cross-resistance, some breast cancer may show total cross-resistance to endocrine therapy. Some Breast tumours may show resistance not only to AI but also to other forms of endocrine therapy.[71] Non-cross resistance, Some breast tumours show resistance to AI but show effective response or sensitivity towards other endocrine therapy,[72] Specific non-cross resistance, Few tumours may show resistance for one AI or one class of AI but shoe response to another AI.[73]

Mechanism of resistance

Ineffective or compromised inhibition of aromatase enzyme

Treatment with AI may sometimes be not sufficient or compromised. This is due to a lack of potency. Complete blockage of estrogen synthesis was not achieved by early generations of AI and the residual estrogen maintains the proliferation of tumour cells in the case of ER+ tumours.[65,74] Poor Pharmacokinetics, Aminoglutethimide catalyzes its metabolism by inducing liver cytochrome P450 enzymes.[75] Drug interaction: AI shows drug interaction with tamoxifen.[76] Concomitant administration of anastrozole or lenestrazole with tamoxifen leads to a decrease in the availability of letrozole by 30-40 % and anastrozole by 20-30% in plasma.[59,77] Compensatory endocrine loop: Ineffective inhibition of AI is also due to the high level of aromatase enzyme as in the case of premenopausal women. In premenopausal women, compensatory endocrine loops result in increased levels of gonadotropins which in turn stimulates the production of androgens and aromatase in the ovaries.[78,79] For use of AI in premenopausal women, concomitant use of luteinizing hormone-releasing hormone (LHRH)agonist which can block the rise in levels of gonadotropins. Mutation: Production of Mutant aromatase molecules that are resistant to AI or showing different sensitivity for different AI is possible.[80]

Exogenous estrogens

AI does not have any effect on exogenous estrogens like synthetic estrogens, industrial pollutants, and

phytoestrogens. Some adrenal androgens that can interact with ER.[81]

Inherent estrogen sensitivity

AI inhibits the synthesis of endogenous estrogen and its action on estrogen receptors. This shows that ais can only be used in the case of ER+ tumours. ER+ tumours may not respond effectively while treating with AI. This may be due to a mutation in the ER.[82] In some ER+ tumours, hereditary material encoding for abnormal or mutant ER is reported and such receptors cannot transmit normal signals on binding with estrogen or estrogen antibodies. These tumours with mutant ER are inherently insensitive to hormone stimulation and therefore do not respond to AI therapy. Abnormality in the signalling pathway of ER like an abnormality in co-regulators may also result in insensitive ER+ tumours.[83,84]

Activation of signalling pathways

Messenger systems are present that can activate ER signalling by low levels of estrogen or in the absence of estrogen. Example: HER Human Epidermal Factor receptor signalling can show phosphorylation of ER even without estrogen and activates the signalling pathway.[85] Other intracellular kinases capable of activating and supersensitized ER signalling include mapks and IGFR/ AKT.[86]

Proliferation and growth of the tumour by estrogen-independent pathway

In some tumours, proliferation and growth of tumour cells are due to stimulation by estrogen-independent pathway. In this type of tumour, ER is normal and regulating estrogen-dependent process but tumour growth is under the influence of the ER independent pathway.[87] Such type of tumours is not affected by AI as they can only cause inhibition of estrogen-regulated pathway.[88]

Cell Survival

Acquired resistance pattern is responsible for the development of cellular clones which can make the therapy ineffective against these clonal cells and they have a survival advantage over cells which are sensitive towards the treatment. Acquired resistant tumours are usually ER+ve and clones have ER.[65,89]

CONCLUSION

Although there are aromatase inhibitors which are available in market for breast cancer, it also be used for ovulation induction in female infertility and gynaecomastia. The success of aromatase inhibitor, developing small biologically active molecule with lower side effects and better tolerability are in process. One of the ways to block synthesis of estrogen is inhibition of aromatase enzyme, as it plays key role in rate limiting step. Since some drugs are in clinical trial pipeline for the treatment of breast cancer, many chemical entities are synthesized as selective inhibitor of aromatase enzyme. Bothersome side effects associated with aromatase inhibitor with long term therapy likely to be their effect on bone density. Although it can be minimised with concomitant use of potent bisphosphonate therapy to reduce bone thinning and osteoporosis. This review aims are facilitating more readers about development of selective, novel, potential chemical entities. Administration of aromatase inhibitors associated with increased level of follicle stimulating harmone (FSH), testosterone and LH. Lowering estradiol levels, therefore increase levels of testosterone in men with low testosterone levels.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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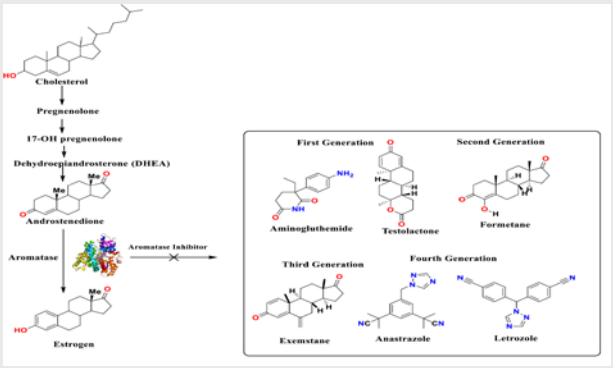
PICTORIAL ABSTRACT



SUMMARY

- One of the best ways to block synthesis of estrogen is inhibition of aromatase enzyme, as it plays key role in rate limiting step.
- It also be used for ovulation induction in female infertility and gynaecomastia.
- The success of aromatase inhibitor, developing small biologically active molecule with lower side effects and better tolerability are in process.
- This review aims are facilitating more readers about development of selective, novel, potential chemical entities.

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