A REVIEW ON AROMATASE INHIBITORS FOR BREAST CANCER

Sandhya Jain, Nidhi J Patel

ITM SCHOOL OF PHARMACVY, ITM (SLS) BARODA UNIVERSITY

ABSTRACT

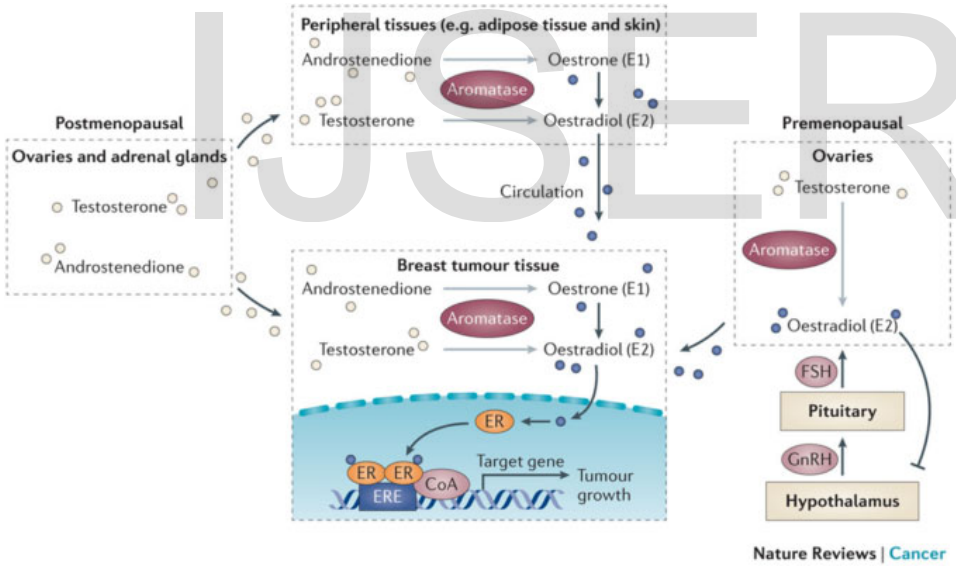
Breast cancer is cancer that forms in the calls of the cells of the breasts. After skin cancer, breast cancer is the most common cancer diagnosed in women in the United States. Breast cancer can occur in both men and women, but it's far more in women. Aromatase inhibitors are the selective therapy for breast cancer Aromatase inhibitors are an anti-estrogen agent that targets specifically the aromatase enzyme. Aromatase, also called estrogen synthetase or estrogen synthase is an enzyme responsible for a key step in the biosynthesis of estrogen. It is CYP19A1, a member of the cytochrome p450 superfamily. Aromatase is responsible for the aromatization of androgen into estrogen.

There are two types of aromatase inhibitors: ***STEROIDAL AND NON-STEROIDAL****.*

In this review, we mainly focus on the mechanism of action, Types, Advantages, Disadvantages, biosynthesis, and resistance of aromatase inhibitors in breast cancer therapy.

KEYWORDS:

Breast cancer, Aromatase inhibitors, Cytochromesp450 (Cyp450), Estrogen synthase



INTRODUCTION

Worldwide breast cancer estimates included over one million incident cases and almost 400,000 deaths in the year 2000 [1,2]. In the United States, over 178,000 women were expected to be diagnosed with breast cancer in 2007 with over 40,000 deaths occurring from the disease [3]. In developed countries, mortality from breast cancer has recently begun to decline, primarily due to earlier detection and improved treatments [4,5]. Breast cancer is thought to be a result of inherited genetic predisposition (e.g., mutations in genes such as BRCA-1, BRCA-2, p53, PTEN/MMAC1, and/or ATM) and/or environmental factors (e.g., radiation exposure, dietary factors, alcohol consumption, hormonal exposure) [2,6,7].

Aromatase inhibitors plays important role in the treatment of breast cancer. Estrogen and its metabolites play a significant role in proliferation of hormone receptor-positive breast cancer. In postmenopausal women, aromatase inhibitors can significantly reduce estrogen levels by blocking enzyme mediated estrogen synthesis within tissues Aromatase inhibitors lower estrogen levels by stopping an enzyme in fat tissue (called aromatase) from changing other hormones into estrogen .(Estrogen can fuel the growth of breast cancer cells) These drug don't stop the ovaries from making estrogen.[8]

The aromatase enzyme found in tissues of endometriosis, uterine fibroids, adipose tissues, a cytochrome p450 enzyme, catalyse the last stage of oestrogen synthesis. Many breast tumour tissues have shown the presence of aromatase enzyme activity forming local oestrogen source [3]

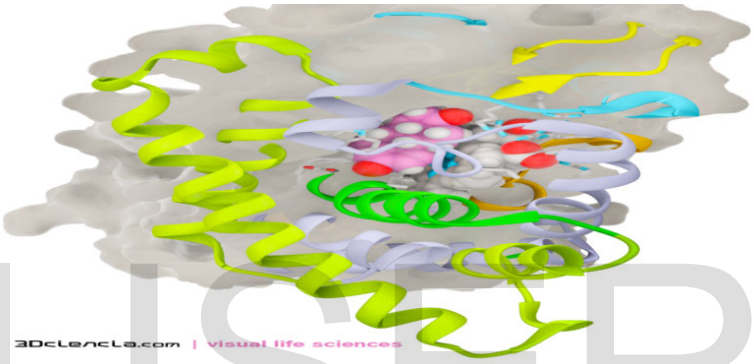


FIG. AROMATASE INHIBITOR

SOURCES OF AROMATASE

Aromatase, an enzyme of the cytochrome P-450 superfamily and the product of the CYP19 gene, [9] is highly expressed in the placenta and in the granulosa cells of ovarian follicles, where its expression depends on cyclical gonadotropin stimulation. Aromatase is also present, at lower levels, in several no glandular tissues, including subcutaneous fat, liver, muscle, brain, normal breast, and breast-cancer tissue.[9,11]]Residual estrogen production after menopause is solely from nonglandular sources, in particular from subcutaneous fat. Thus, peripheral aromatase activity and plasma estrogen levels correlate with body-mass index in postmenopausal women.[12] At menopause, mean plasma estradiol levels fall from about 110 pg per millilitre (400 pmol per liter) to low but stable levels of about 7 pg per milliliter (25 pmol per liter). In postmenopausal women, how ovulation in women with infertility. [10] The data in the current review, however, pertain solely to postmenopausal women

MECHANISM OF AROMATASE INHIBITORS:

Conversion of androgens to oestrogens by aromatase comprises of three sequential oxidation steps, each one requiring 1 mol of O2 and NADPH [13]. In the first step, the androgen is hydroxylated at C-19 to afford the 19 - hydroxy intermediate. The reaction occurs with the retention of configuration, which is characterised by a significant normal kinetic isotope effect. In the second step 19 - hydroxy steroid undergoes second hydroxylation of C-19 to give gem diolic group. This on consequent dehydration results in the corresponding aldehyde. While there is enough evidence to explain the first and the second steps, the supposed oxidative cleavage of bond between C10 and C19 to afford estrogen and formic acid in the third step is not clear [14, 15]. A recent investigation proposes that the third step also follows the ferroxy radical mechanism as the first two steps [16]

Aromatase inhibitor tamoxifen inhibits the growth of the breast tumor by the competitive antagonism of estrogen at estrogen receptor site. It also possesses partial agonistic properties. These agonistic properties of tamoxifen are detrimental to the expected clinical efficacy since they are associated with contrast aromatase inhibitors suppressive estrogen synthesis by inhibiting aromatase enzyme and also are devoid agonistic problems genrally associated with antiestrogenic.

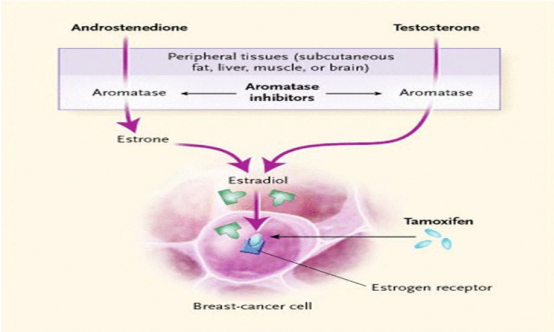


Fig. MOA OF AROMATASE INHIBITORS

TYPES OF AROMATASE INHIBITORS:

Aromatase inhibitors mainly dived into two categories:
TYPE 1(STERODIAL)
TYPE 2(NON-STERODIAL)

TYPE 1(STERODIAL AROMATSE INHIBITORS)

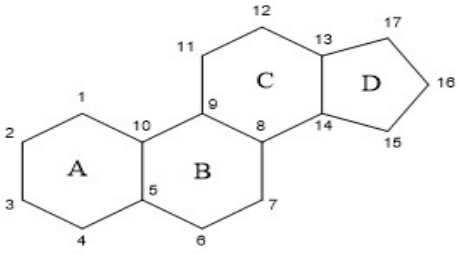
Steroidal aromatase inhibitors are a class of drugs that are mostly used for treating breast cancer in postmenopausal women. High levels of estrogen in breast tissue increase the risk of developing breast cancer and the enzyme aromatase is considered to be a good therapeutic target when treating breast cancer due to it being involved in the final step of estrogen biosynthetic pathway and also its inhabitation will not affect the production of other steroids.

Competitive enzyme inhibitors. Investigations on the development of aromatase inhibitors began with the synthesis and biochemical evaluation of competitive inhibitors (17-19). The term “apparent Ki” represents the equilibrium constant for the reversible binding of the enzyme and the inhibitor. The values are used in comparisons of inhibitors, and the smaller the value, the better the inhibitor

***MECHANISM OF STEORDIAL AROMASTE INHIBITORS*:**

Steroidal aromatase inhibitors irreversibly inhibit the enzyme by binding covalently to the binding site of aromatase so the substrate can't access it. These inhibitorsbindtothearomatasecytochromeP450enzymein the same manner as the substrate androstenedione.

STRUCTURE:

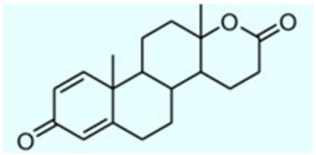
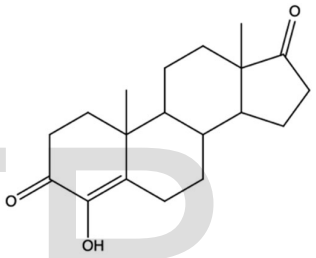
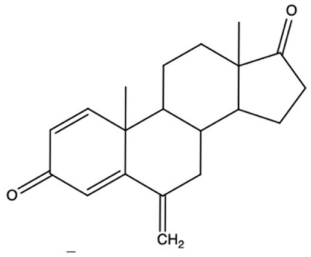


CLINICAL USE

Cancer

A majority of breast cancers are hormone-dependent and most of them express either the estrogen receptor and/or progesterone receptor [21][22][23]. That is the reason that compounds that inhibit the biosynthesis of estrogen have been researched and are now the standard adjuvant therapy for breast cancer in postmenopausal women [21][22]. Brain, skin, adipose tissue, normal breast tissue, and breast cancer cells have aromatase but estrogen that is synthesized in breast tissue and around the cancer cells affects the growth of cancer. Aromatase inhibitors stop this conversion and lower the levels of estrogen.

EXAMPLE OF STERODIAL AROMATASE INHIBITORS

GENERATION	TYPE 1	STRUCTURE
First	Testolactone	
Second	Formestane	
Third	Exemestane	

V. NONSTERODIAL AROMATASE INHIBITORS:

NSAIs is mainly used to treat breast cancer in women. NSAIs binding is a reversible process where NSAIs binds to the aromatase enzyme through non-covalent interactions. NSAIs are used to treat hormone-dependent breast cancer. all cancer cells express either estrogen or progesterone receptors it is a possibility that and-estrogen treatment work. The binding of the NSAIs depends on the binding site of the aromatase as it has to fit into the substrate-binding site of the aromatase enzyme. NSAIs are not as specific as SAIs and therefore other enzymes may be inhibited which also have cytochrome P450 groups. It has been possible to develop selective drugs against cytochrome P450 aromatase where the amino acid sequence of the P450 from is well defined from other members of the P450 cytochrome family, resulting in more specific inhibition of the aromatase [24].

Aminoglutethimide was the prototype for nonsteroidal aromataseinhibitors [25]. Aminoglutethimide was originally an antiepileptic agent that was removed from the market due to serious side effects. Aminoglutethimide inhibited cytochrome P450SCC and other enzyme pathways but was more selective for cytochrome P450arom. The racemic mixture (dl-aminoglutethimide) inhibits aromatase with an apparent Ki of 700 nm. The d-aminoglutethimide stereoisomer is 20-fold more potent than the l-aminoglutethimide stereoisomer

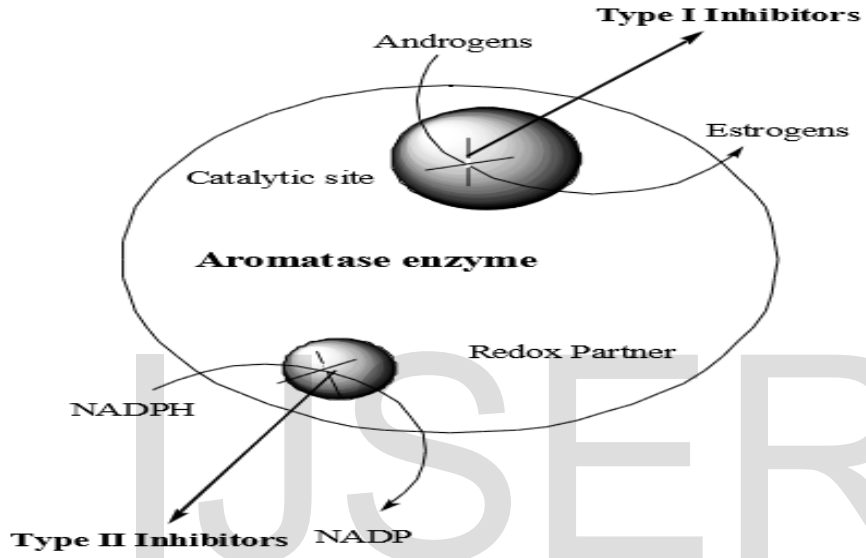
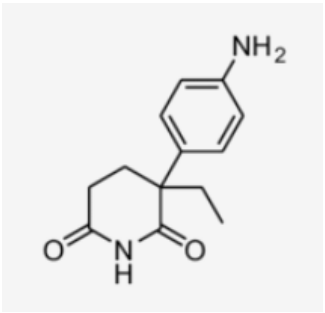
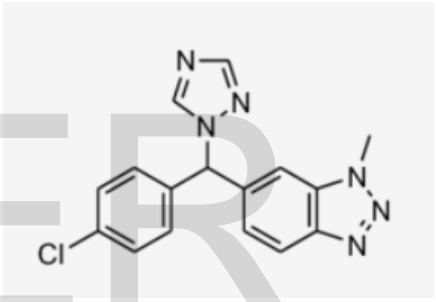
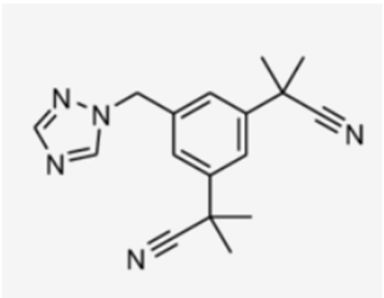


Fig. (2). Mechanism of type I and II aromatase inhibitors.

MOA OF NSAIs

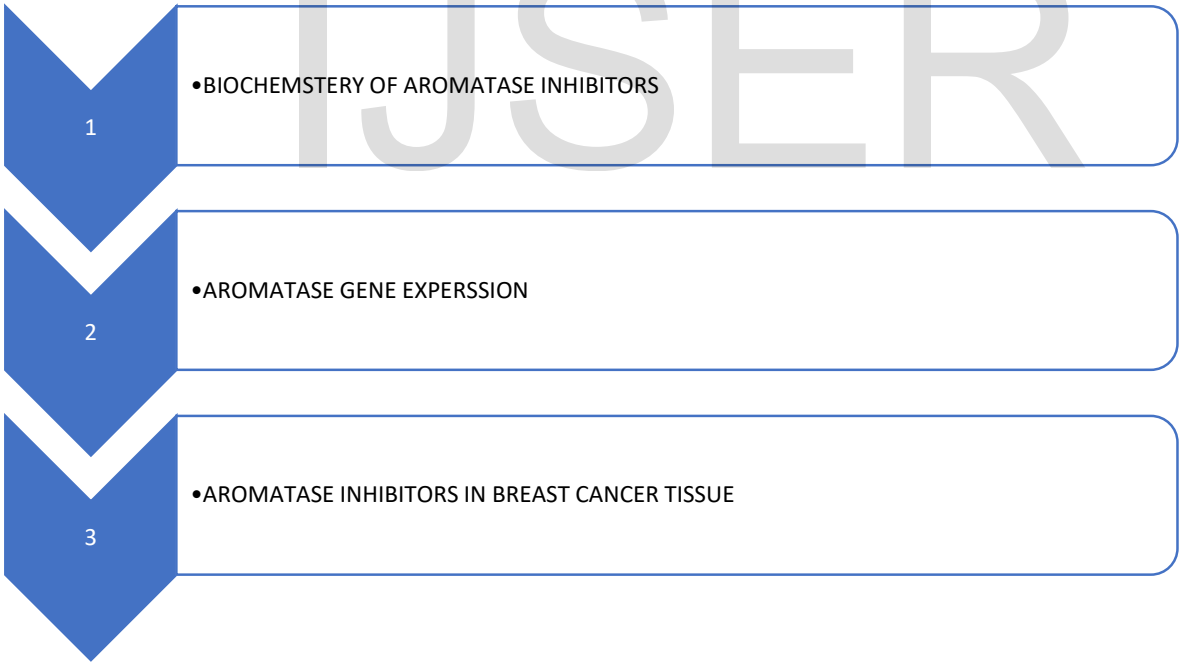
NSAIs is a reversible binding process where NSAIs binds to the aromatase enzyme through non-covalent interactions [26]. NSAIs does not destroy the enzyme-like SAIs do. An interaction occurs with a heme group of cytochrome P450 in the aromatase enzyme [24]. The first- and second-generation of NSAIs, aminoglutethimide, and fadrozole also have a reducing effect on the production of aldosterone and cortisol. The third generation, anastrozole, and letrozole are very selective, they only inhibit the aromatase enzyme and do not affect other steroidogenic pathways [27]. Mechanism of NSAIs is a reversible binding process where NSAIs binds to the aromatase enzyme through non-covalent interactions [26].

EXAMPLE OF NSAIs:

GENERATION	TYPE 2	STRUCTURE
FIRST	Aminoglutethimide	
SECOND	Vorozole	
THIRD	Anastrozole	

NON-COMPETITIVE	COMPETITIVE
Steroidal	Non-Steroidal
Daily administration	Daily administration
Covalent bond irreversibly inactivates an enzyme	Reversibly binds to the active enzyme binding site
Enzyme actively is restored by new enzyme synthesis	Enzyme binding depends on relative concentrations and affinities of inhibitors and substrate
Partial lack of cross-resistance with non-steroidal inhibitors	

BIOSYNTHESIS OF AROMATASE INHIBITORS

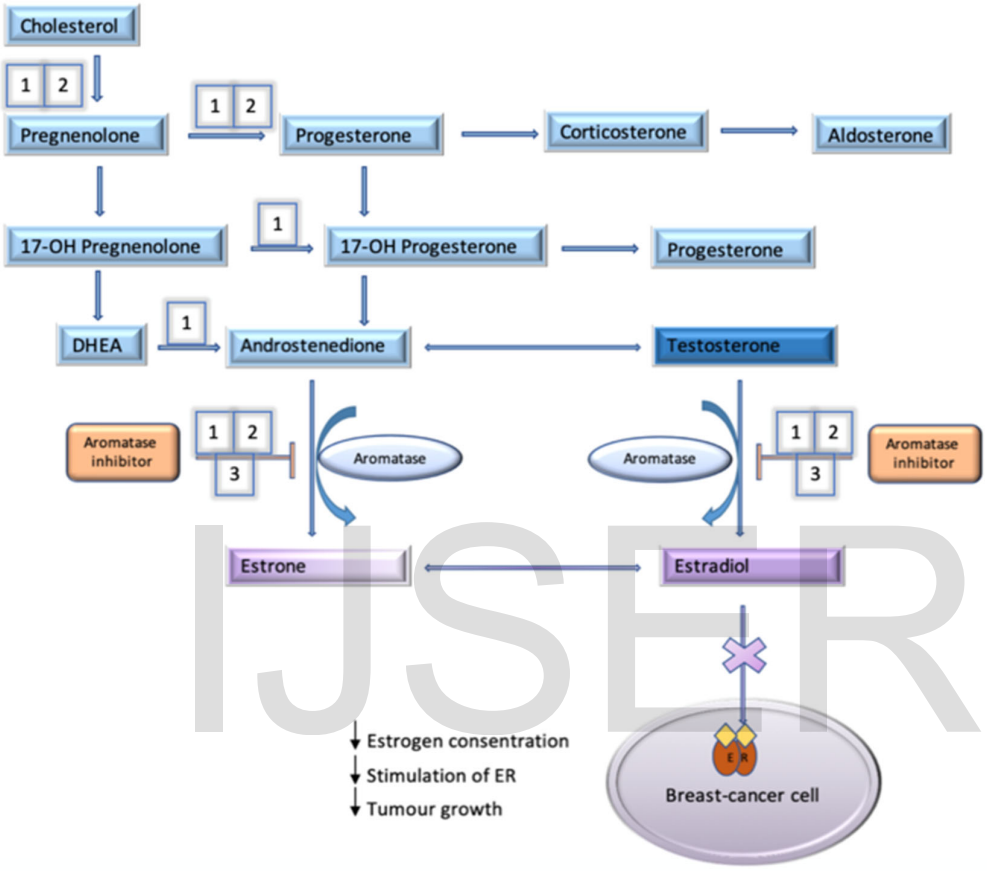


BIOCHEMISTRY OF ARMATASE INHIBITORS

Aromatase, a member of the cytochrome P450 (CYP) enzyme family, is a product of the $:1 gene and is the rate-limiting step in the conversion of androstenedione to estrone and of testosterone to estradiol [28]. The $:1gene is highly expressed in the human placenta and the granulosa cells of the ovarian follicles. Nonglandular tissues having lower levels of aromatase activity include subcutaneous, fat, liver, muscle, brain, normal breast, and breast cancer tissues [29]. The activity of the enzyme is increased by alcohol, advanced age, obesity, insulin, and gonadotropins [29]. Recent advances in computational chemistry, including density functional theory alone or in combination with molecular mechanical methods, have provided better tools that enable the study of the active species in their native protein environment, such as the cytochrome P450 oxidant Compound I [30].

Aromatase gene expression

Over the past two decades, knowledge of biochemistry, molecular biology, and regulation of aromatase has increased greatly. The aromatase gene, designated CYP19, encodes the cytochrome P450arom, and this gene is located on chromosome15q21.1. The coding region is approximately30 kb in size, and the regulatory region is approximately 93 kb [31, 32] The aromatase gene consists of 10 exons, and its full-lengthcDNAof3.4kbencodesforaproteinof503amino acids. The aromatase protein is a glycosylated cytochrome P450 protein with a molecular mass of approximately 58,000 Da [33].



METABOLIC PATHWAY FOR ESTROGEN PRODUCTION:

Aromatase in breast cancer tissues

Aromatase is found in breast tissue, and the importance of intratumoural aromatase and local estrogen production is being unravelled [34, 35, 36] Aromatase has been measured in the stromal cell component of normal breast and breast tumours, but the enzyme has also been detected in the breast epithelial cells in vitro [37, 38, 36–39]. Furthermore, the expression of aromatase is highest in or near breast tumour sites [38,36]. The exact cellular location(s) of aromatase must await a more rigorous analysis by several laboratories with a new monoclonal antibody now being developed and evaluated [40]. The increased expression of aromatase cytochrome P450arom observed in breast cancer tissues is associated with a switch in the major promoter region used in gene expression, with promoter PII being the predominant promoter used in breast cancer tissues [41]. As a result of the use of the alternate promoter, the regulation of estrogen biosynthesis switches from one controlled primarily by glucocorticoids and cytokines to a promoter regulated through cAMP-mediated pathways [41]. Prostaglandin E2 (PGE2) increases intracellular cAMP levels and stimulate estrogen biosynthesis [41], whereas other autocrine factors such as IL B(Beta) appear to act via Pge2 [42].

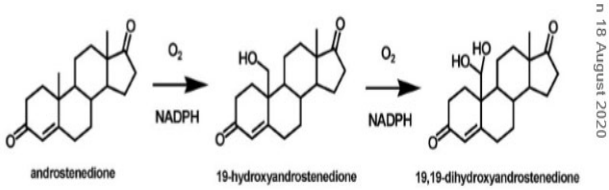
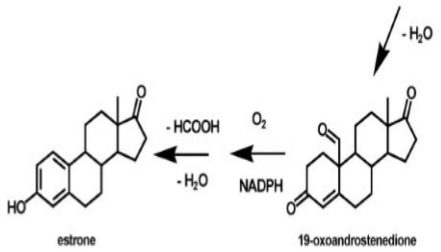


FIG. 1. Aromatase enzyme reaction



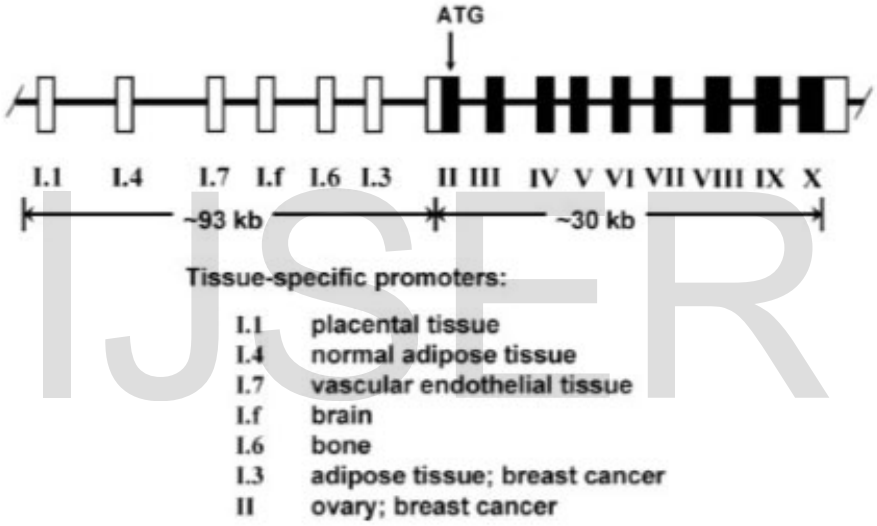
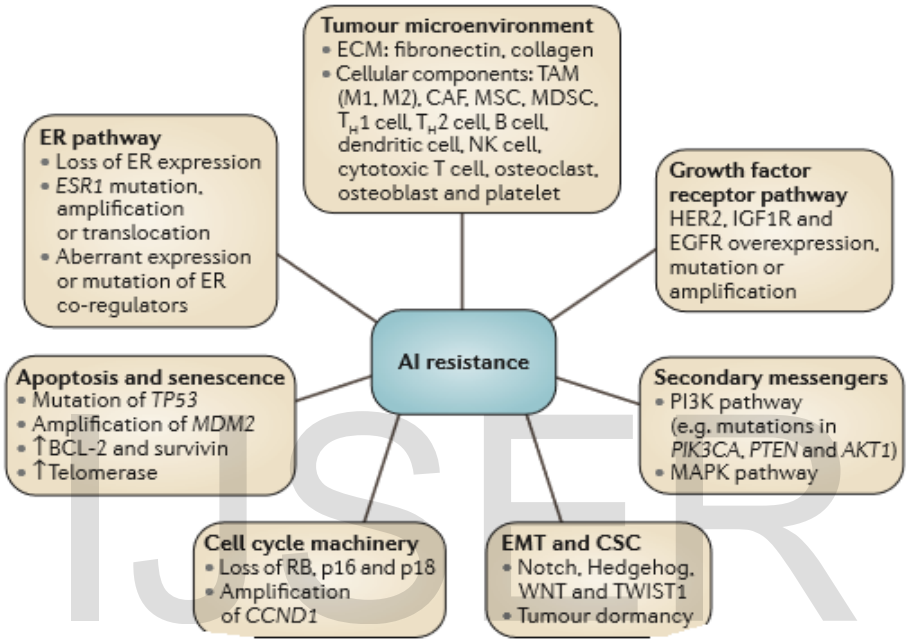


FIG. 3. Aromatase gene and promoter regions.

MECHANISM OF RESISTANCE OF AROMATSE INHIBITORS:

Aromatase inhibitors (AIs) have a central role in the treatment of breast cancer; however, resistance is a major obstacle to optimal management. Besides the therapeutic success of the third-generation AIs, acquired resistance may develop, leading to tumour relapse. This resistance is thought to be the result of a change in the behaviour of ER in these breast cancer cells, presumably by PI3K/AKT pathway enhancement along with alterations in other signalling pathways. Nevertheless, biological mechanisms, such as apoptosis, autophagy, cell cycle modulation, and activation of androgen receptor (AR), are also implicated in acquired resistance. Moreover, clinical evidence demonstrated that there is a lack of cross-resistance among AIs, although the reason is not fully understood. Thus, there is a demand to understand the mechanisms involved in endocrine resistance to each AI, since the search for new strategies to surpass breast cancer acquired resistance is of major concern.

TYPES OF RESISTANCE



CILINICAL VERUS OTHER FORMS OF RESISTANCE

PRIMARY VERUS ACQUIRED RESISTANCE

CROSS RESISTANCE AND NON CROSS RESISTANCE

DEFINITION:

I. *Clinical versus other forms of resistance*:

Clinical 'resistance' to AIs is usually perceived as a lack of growth inhibition by AI treatment in that the therapy is ineffective in causing a decrease in tumour size. However, AI treatment often results in molecular (and pathological) changes in clinically resistant tumours [43,44]. Clinical resistance, therefore, needs to be distinguished from other forms of resistance, including that in which AI therapy fails to elicit any form of response (in the same way as dependence should be separated from sensitivity).

I. *Primary versus acquired resistance*:

Resistance may be subdivided into primary (or de novo) and secondary to initial treatment response (or acquired). Although having clinical implications, primary and acquired resistance may not be separate entities and underlying mechanisms of resistance may be shared. However, the inference is that 'acquired' resistance is the result of inductive changes or clonal selection caused by treatment. Molecular changes that could impact on eff effectiveness of therapy have been observed following AI treatment [45,46].

***Cross-resistance and non-cross-resistance**:*

Some tumours resistant to AIs also appear non-responsive to other forms of endocrine therapy (that is, they are cross-resistant [47] other AI resistant tumours are sensitive to other endocrine therapies (that is, there is no cross-resistance [48,49]. Non-cross-resistance can be subtle where, for example, tumours may be resistant to one AI (or class of AIs) but respond to another [50,51].

By analysing information about the genetic, molecular biology and physiology of cancer cells, the models allocate the key molecules that were associated to the development of AIs resistance, both in vitro and in vivo, in 'decision modules' (cell cycle and apoptosis), 'stress modules' (autophagy and unfolded protein response) and 'signal processing modules' (ER and growth factor signalling). As the majority of acquired endocrine resistance cases occur in ER-expressing breast cancers, it is suggested that loss of ER expression is not the main mechanism. This evidence reinforces the need to understand the molecular processes to design new strategies to overcome AIs-acquired resistance.

Evaluation of AIs with other forms of endocrine therapies:

The third AIs (anastrozole, letrozole, and exemestane) have greater ability and improved safety profiles compared with their predecessors when employed as a treatment for hormone-responsive postmenopausal breast cancers [52, 53, and 54]. Randomized clinical trials also show that third-generation AIs are equivalent or larger in efficiency to tamoxifen [55,56,57,58] and maybe effective in tamoxifen-resistant advanced breast cancer [59,60]. Although the latter observation, prior resistance to other forms of endocrine therapy is associated with a decreased probability of response to an AI [61]. It is worth commenting on the time taken to elicit a clinical response. Several neoadjuvant protocols show that longer treatment with AI results in an additional clinical benefit [62,63]. It is thus possible that a minority of apparently resistant tumours may be sensitive to the action of AIs but extended treatment is required before clinical response becomes manifest. This contrasts with the speed of response generally observed following chemotherapy.

Letrozole-resistant

Several mechanisms that involve MAPK and PI3K pathways and cell cycle regulators are linked to letrozole acquired resistance. Letrozole-resistant cells exhibit reliance on the MAPKs pathways, mainly through HER2 and EGFR overexpression [64], which highlights the part of GFRs on the ligand-independent activation of ER Co-targeting HER2, via trastuzumab, and ER signalling, in long-term letrozole-treated tumour (LTLT-Ca) cells, a resistant cell model, restored letrozole sensitivity, inducing tumour regression as a consequence of a re-expression of ER [65]. Nevertheless, recent data also defined that letrozole-resistant cells present a higher expression/activation of the PI3K/AKT/mTOR pathway. In a reported phase, I trial [68], the inhibitor buparlisib showed to be safe and to have anti-tumour efficacy in combination with letrozole [67] Altered PI3K inhibitors, such as pilaralisib and voxtalisib, are currently being tested in phase I/II studies Moreover, in letrozole-resistant cells, taselisib, also a PI3K inhibitor, demonstrated anti-tumour efficacy in combination with letrozole Recent studies [68] have also described an association with cell cycle regulation and letrozole resistance [70,71]. FDA recently approved as first-line treatment in ER+ postmenopausal women the inhibition of CDK 4/6 with palbociclib in combination with letrozole [69]. This approach showed high efficacy, as previously described by the PALOMA-1/TRIO-18 clinical trial, and the ability to prevent letrozole resistance an up-regulation of Aurora kinase A and B also seems to be involved in letrozole acquired resistance. Their embarrassment resulted in tumour growth suppression, specifying that these kinases might be new potential therapeutic targets [72]. Moreover, studies involving the histone deacetylase (HDAC) inhibitor, entinostat, suggested a beneficial effect, from side to side HER2 modulation, on LTLT-Ca cells and Letrozole-resistant MCF-7Ca xenografts [74,75].

Anastrozole resistance

Altered mechanisms were designated to be associated with anastrozole resistance, and most of these seem to share the same growth factor receptor eccentricity. Anastrozole-resistant cells do not exhibit an up-regulation in HER2 like in letrozole resistance Instead, they present an intensification in IGFR1 and a reduction in ER expression and aromatase activity, with up-regulation of the PI3K/AKT pathway [76,75]. In fact, a study conducted by Rechoum et al. showed that overexpression of AR and collaboration amid AR and ER led to anastrozole resistance of MCF-7 cells that overexpress aromatase and AR, through the activation of IGF1R and

PI3K-AKT pathways. Consistently, the use of an IGF1R inhibitor, AG1024, or a dual kinase AKT inhibitor, Akti 1/2, restored sensitivity to anastrozole Similar results were found using the AKT/mTOR inhibitor MK-2206, on anastrozole-resistant cells consequent from aromatase-overexpressing MCF-7 [81] cells and the PI3K inhibitor pictilisib on phase II randomized trial [77] Therefore, it can be concluded that targeting the PI3K/AKT/mTOR pathway in anastrozole resistance is of major importance. This was strengthened by the use of a MAPK inhibitor, selumetinib, which caused downregulation of activated MAPK and phosphorylated mTOR, reverting anastrozole resistance.

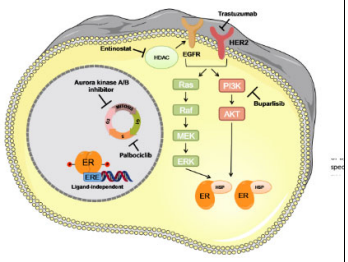
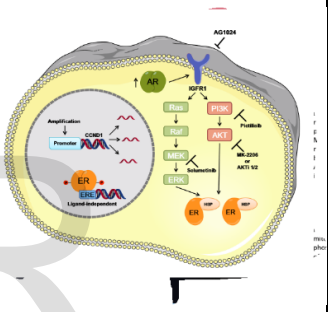
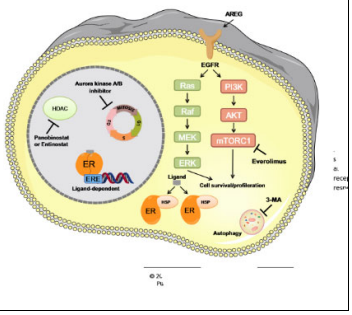
Moreover, in a TransATAC study, it was pragmatic that amplification of the CCND1, a gene that encodes cyclin D1, was associated with an increased risk of tumour recurrence in response to anastrozole. The biological effects of the combination of a CDK 4/6 inhibitor, abemaciclib, plus anastrozole vs anastrozole or abemaciclib alone, are being evaluated by the ongoing EO monarch clinical trial.

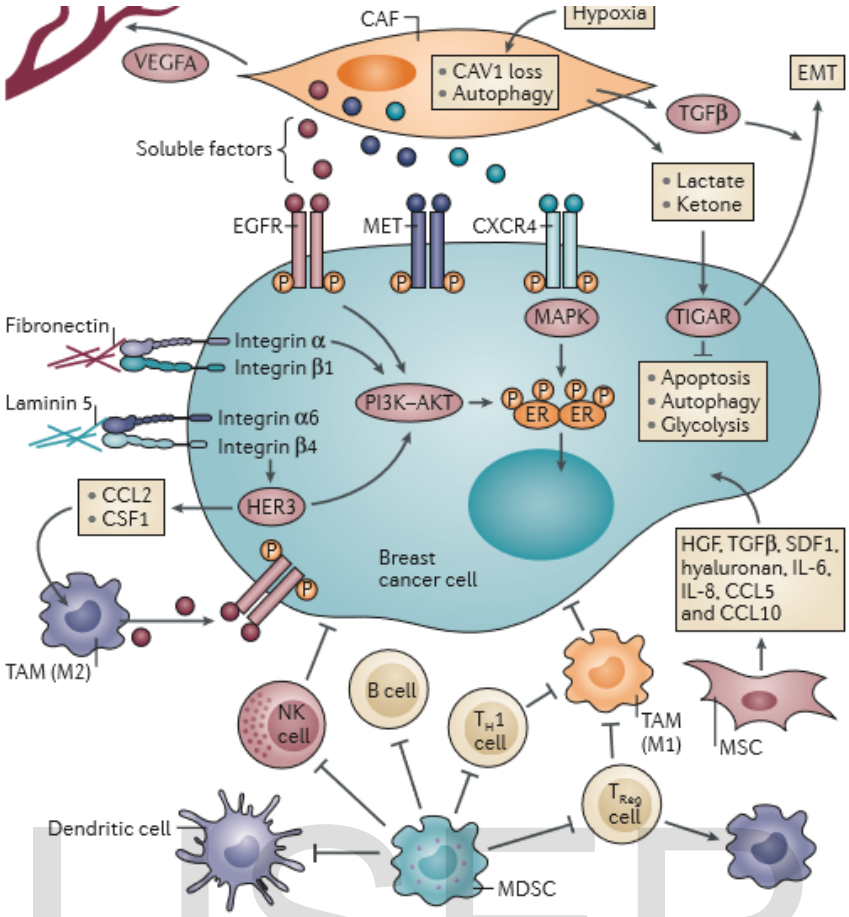
Exemestane resistance

Exemestane, the only steroidal AI of the third-generation group, has an altered resistance mechanism when compared to the two non-steroidal AIs Contrary to non-steroidal AI-resistant cells, Exemestane-resistant cancer cells carry on to present a hormone-dependent behavior In the last years, different mechanisms have been supplementary with exemestane innate resistance, with some of them being corporate to non-steroidal AIs while others are speciously specific for this steroidal AI. exemestane resistance is the upregulation of the cell cycle regulators, Aurora kinase A and B, in resistant cells derived from MCF-7 cells Moreover, a recent phase III study is currently evaluating the efficacy of palbociclib, in combination with Exemestane or fulvestrant, vs capecitabine. Genetic and epigenetic alterations are also known to play a role in exemestane resistance. HDAC inhibitors also seem to reverse exemestane resistance in resistant cells derived from MCF-7-aro cells. In this study, the HDAC inhibitor, panobinostat, inhibited exemestane-resistant cancer cell proliferation, through cell cycle arrest, and apoptosis. Similarly, the use of the HDAC inhibitor, entinostat, has also shown promising results in a randomized phase II, double-blind, placebo-controlled study, for this reason, this combination is now being studied in phase III clinical trial.

Finally, autophagy is also an alternative potential mechanism associated with exemestane resistance, since it appears to act as a pro-survival mechanism. Our group described that the combination of the autophagic inhibitor, 3-methyladenine (3-MA), with exemestane re-sensitized resistant breast cancer cells). A recent analysis, in ER+ carcinoma cells of patients following adjuvant exemestane treatment, demonstrated an increase in the immunoreactivity of autophagic markers, LC3 and beclin-1, and a correlation between beclin-1 levels in pre-treated stromal cells and poor clinical response to endocrine therapy (Ueno et al. 2016). Thus, this highlights the autophagic process as an important player to overcome resistance, to achieve therapeutic success.

SUMMARY TABLE OF the MAIN MECHANISM OF ACQUIRED RESISTANCE TO THIRD GENERATION AIs.

ADAPTATION	MECHANISM OF RESISTANCE	IMAGE
Letrozole resistance HER2 overexpression PI3K/AKT/mTOR overexpression CDK4/6 activity Cyclin E overexpression Aurora kinase A/B upregulation HDAC aberrant activity	Decrease expression and ligand-independent activation of ER Decrease expression and ligand-independent activation of ER Raise of cell cycle progression Promotion of cell cycle probation Promotion of cell cycle progression HER2 modulation	
Anastrozole resistance IGFR1 overexpression PI3K/AKT/mTOR overexpression MAPK overexpression Androgen receptor overexpression CCND1 amplification	Decrease expression and ligand-independent activation of ER Decrease expression and ligand-independent activation of ER Decrease expression and ligand-independent activation of ER Increase IGF1R and PI3K/AKT/mTOR signalling Promotion of cell cycle progression	
Exemestane resistance AREG overexpression Aurora kinase A/B up-regulation HDAC aberrant activity Autophagy	Increase MAPK pathway activity Promotion of cell cycle progression NF-κB expression Pro-survival cellular mechanism	



THE TUMOUR MICROENVIRONMENT AND AI RESISTANCE

ADVANTAGES & DISADVANTAGES OF AROMATASE INHIBITORS AND:

Type of inhibitor	Advantages	Disadvantages
Steroidal inhibitor	More selective Longer half life Less toxic	Poor oral bioavailibility Androgenic effects on high doses Metabolism by other CYP 450 enzymes
Non steroidal inhibitors	Highly potent Good Pharmacokinetic profile Lack of hormonal properties	Less selective Musculoskeletal problems

FUTURE DEVELOPMENT

Through now third-generation aromatase inhibitors are alternative to tamoxifen but left some room for improvement. There is a need for the appearance of fourth-generation aromatase inhibitors with unambiguous aromatase inhibition and low toxicity profiles exclusively for addressing musculoskeletal disorders. There should be more clinical trials of in effect aromatase inhibitors to doggedness problems like the role of aromatase inhibitors in chemoprevention and clinical response among the third-generation agents. In future clinical studies, it is important to test ER receptor status, receptor coactivators, and ErbB-2 for superior treatment methodology. Combination therapy of aromatase inhibitors along with agents targeting other molecular targets like COX-2 inhibitors may influence the efficacy of aromatase inhibitors, recently some studies were planned for this purpose. Current clinical data supports letrozole's ability to induce monofollicular ovulation it is desirable for patients with polycystic ovarian syndrome. As the medicinal chemistry of aromatase inhibitors attaining maturity, there are new trends. Recently, Lawrence et al reported dual aromatase steroid-sulfatase inhibitors Some of the chromone and xanthone derivatives have shown inhibitory activity on both aromatase and C17, 20 lyases Such type of molecules may provide more therapeutic assistance and manifold clinical presentation

CONCLUSION:

Aromatase inhibitors are at this time designated as first-line adjuvant endocrine therapy in the treatment of early-stage breast cancer in postmenopausal women with ER-positive tumours. The efficacy of these medications in prolonging disease-free survival and decreasing the risk of contralateral breast cancer has led to a considerable increase in the frequency of their use. Many of the adverse effects associated with these medications may be more readily recognized by physicians familiar with the adverse effect profiles of these drugs. Reducing the severity and frequency of adverse effects may improve the quality of life for patients taking AIs and prevent discontinuation of this well-documented and beneficial therapy. Undesirable longterm effects such as fractures can be prevented with appropriate recognition and treatment The FDA approvals for the delay in tumour progression achieved by everolimus and the CDK4 and CDK6 inhibitor palbociclib in combination with an AI promote optimism that considerable improvements in the treatment of AI therapy-resistant ER+ breast cancer are a near-term possibility. However, there is currently no evidence to date that these dual-targeting approaches improve overall survival or are active adjuvant treatments. Improvements in the fidelity of preclinical models are therefore essential, and PDX models have a role in moving the endocrine resistance field beyond the restricted discovery space afforded by the few ER+ cell lines available31. However, the value of PDX models for the study of tumour dormancy, stem cell-like behavior, and stromal–epithelial interactions is Unclear.

REFERENCE:

[1]. Ferlay, J.; Bray, F.; Pisani, P.; Parkin, DM. GLOBOCAN (2000): Cancer Incidence, Mortality and Prevalence Worldwide, IARC Cancer Base No. 5. International Agency for Research on Cancer (IARC) Press; Lyon: 2001.

[2]. Parkin DM. Lancet Oncol. (2001); 2:533. [PubMed: 11905707]

[3]. Jemal A, Siegel R, Ward E, Murray T, Xu JQ, Smigal C, Thun MJ. CA Cancer J. Clin. (2006); 56:106. [PubMed: 16514137]

[4]. Hermon, C.; Beral, V(2001). Breast Cancer: New Horizons in Research and Treatment. Tobias, JS.; Houghton, J.; Henderson, IC., editors. Oxford University Press; New York: p. 3-11.

[5]. Jatoi I, Miller AB. Lancet Oncol. (2003); 4:251. [PubMed: 12681269]

[6]. Mills, GB; Rieger, PT. (2001) the M. D. Anderson Cancer Care Series: Breast Cancer. Hunt, KK.; Robb, GL.; Strom, EA.; Ueno, NT. editors. Springer-Verlag; New York: . p. 55-92.

[7]. Peto J. Nature. (2001); 411:390. [PubMed: 11357148]

[8].https://www.cancer.org>cancer

9 Evans CT, Ledesma DB, Schulz TZ, Simpson ER, Mendelson CR. Isolation and characterization of a compel

10. Mitwally MF, Casper RF (2002). Aromatase inhibition for ovarian stimulation: future avenues for infertility management. Curr Opin Obstet Gynecol 2;14 :255 -63mentary DNA specific for human aromatase-system cytochrome P-450 mRNA. Proc Natl Acad Sci U S a 1986; 83: 6387-91.

11. Miller WR, Hawkins RA, Forrest AP. Significance of aromatase activity in human breast cancer. Cancer Res 1982; 42: Suppl: 3365s-3368s.

12. Nelson LR, Bulun SE. Estrogen production ion and action. J Am Acad Dermatol (2001) 45: Suppl: S116-S124. 27. Longcope C, Baker R, Johnston CC Jr. Androgen and estrogen metabolism: relationship to obesity. Metabolism 1986; 35: 235-7

[13] Thompson, E.A. Jr.; Siteri, P.K. J. Biol. Chem., (1974), 249, 5373.

[14] Cole, P.A.; Robinson. C.H. J. Med. Chem., 1990, 33, 2933.

[15] Akthar, M.; Wright. J.N. Steroids, (1990), 55, 142.

[16] Ahmed S. J. Mol. T Struct (heochem), 1998, 422, 271

[17]. Schwarzel WC, Kruggel WG, BrodieHJ1973 Studies on the mechanism of estrogen biosynthesis 8.Thedevelopment of inhibitors of the enzyme system in human placenta. Endocrinology 92:866–880

[18] Siiteri PK, Thompson EA (1975) Studies of human placental aromatase. J Steroid Biochem 6:317–322

[19] Brueggemeier RW, Floyd EE, Counsell RE (1978) Synthesis and biochemical evaluation of inhibitors of estragon biosynthesis.JMed Chem 21:1007–1011

[20] V an Asten, K.; Ne v en, P.; Lintermans, A.; Wildiers, H.; P aridaens, R. (2014). "Ar omatase inhibitors in the breast cancer clinic: focus on ex emestane " Endocrine-Related cancer. 21 (1): R31–R49. Do i: 10 .1530/ Er c-13- 0269 PMID 24434719

[21] Bedford , M.; Tumur , I.; Chakr abarti, J.; Bar den, J.; Rao, N.; Makris, A. (2011). "A qualitative systematic review of the evidence base for non-cross resistance between steroidal and non-steroidal aromatase inhibitors in metasta breast cancer" Clin Oncol (R Coll Radiol). 23 (3): 209–215. Doi : 10.1016/j. clon. 2010.11.005. PMID 21134732

[22] Chumsri, S (2015). "Clinical utilities of aromatase inhibitors in breast cancer" Int J Women's Health 7: 493–499. Doi 10 . 2147 /IJWH .S69907 PMC 4427607 PMID 26005359

[23] Miller, W. R.; Bar tlett, J.; Br odie, A. M. H.; Brueggemeier , R. W.; Di Salle, E.; Lonning, P. E.; Goss, P. E. (2008). "Aromatase inhibitors: Are there differences between steroidal and non-steroidal ar omatase inhibit ors and do the y matter?" Oncologist. 13 (8): 829–837. doi:10.1634/theoncologist.20080055. PMID 18695261

[24] P arnham, Michael J.; Bruinv els, Jacques (2008). Ar omatase Inhibitors. Basel, Switz erland: Birkhäuser . pp. 2, 4. ISBN 978-3-76438693-

[25] Cocconi G 1994 First generation aromatase inhibitors—aminoglutethimide and testololactone. Breast Cancer Res Treat 30:57–80

[26] Kang, Hongjun; Xiao, Xingqing; Huang, Chao; Y uan, Y an; T ang, Dongy an; Dai, Xiaochang; Z eng, Xianghui (2018-01-01). "potent ar omatase inhibit ors and molecular mechanism of inhibit or y action ". E ur open Journal of Medicinal Chemistry y. 143: 426–437. doi:10.1016/j.ejmech.2017.11.057. ISSN 0223-5234. PMID 29202405 .

[27] Fabien, C. J. (2007-12-01). "The what, why and how of ar omatase inhibit ors: hormonal agents for treatment and prevention of breast cancer ". International Journal of Clinical practice. 61 (12): 2051–2063. doi:10.1111/j.17421241.2007.01587.x. ISSN 13685031. PMC 2228389. PMID 17892469

[28] Ghosh D, Griswold J, Erman M, Pangborn W.(2009) Structural basis for androgen specificity and oestrogen synthesis in human aromatase. /BUVSF. ;457(7226):219-223

[29] Smith IE, Dowsett M. (2003) Aromatase inhibitors in breast cancer. /&OHM+ .FE. ; 348(24):2431-2442

[30] Meunier B, de Visser SP, Shaik S (2004) Mechanism of oxidation reactions catalyzed by cytochrome p450 enzymes. Chem Rev 104: 3947–3980

[31] Meunier B, de Visser SP, Shaik S (2004) Mechanism of oxidation by cytochrome p450 enzymes. Chem Rev 104: 3947–3980

[32] Bulun SE, Takayama K, SuzukiT, SasanoH, YilmazB, Sebastian S (2004) Organization of the human aromatase p450 (CYP19) gene. Semin Reprod Med 22:5–9

[33] Gartner CA, Thompson SJ, Rettie AE, Nelson SD 2001 Human aromatase in high yield and purity by perfusion chromatography and its characterization by difference spectroscopy and mass spectrometry. Protein Expr Purif 22:443–454

[34] Miller WR, O'Neill J (1987) the importance of local synthesis of estragon within the breast. Steroids 50:537–548

[35] Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Corbin CJ, Mendelson CR 1993 Tissue-specific promoters regulate aromatase cytochrome P450 expression. J Steroid Biochem Mol Biol 44:321–330

[36] Miller, Mullen, SourdaineP, WatsonC,DixonJM,Telford J (1997) Regulation of aromatase activity within the breast. J Steroid Biochem Mol Biol 61:193–202

[37] Yates VH, McNeill JM, Lai LC, Newton CJ, Ghilchik MW, Reed MJ(1987) Aromatase activity in normal breast and breast tumor

[38] BulunSE,PriceTM,AitkenJ,MahendrooMS,SimpsonER(1993) A link between breast cancer and local estragon biosynthesis suggested by quantification of breast adipose tissue aromatase cytochrome P450 transcripts using competitive polymerase chain reactionafterreversetranscription.JClinEndocrinolMetab77:1622– 1628

[39] Quinn AL, Burak WE, Brueggemeier RW (1999) Effects of matrix component son aromatase activity in breast stromal cellsinculture. J Steroid Biochem Mol Biol 70:249–256

[40] Sasano H, Edwards DP, Anderson TJ, Silverberg SG, Evans DB, Santen RJ, Ramage P, Simpson ER, Bhatnagar AS, Miller WR (2003) Validation of new aromatase monoclonal antibodies for immunohistochemistry: progress report. J Steroid Biochem Mol Biol 86:239–244

[41] Zhao Y, Agarwal VR, Mendelson CR, Simpson ER(1996) Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. Endocrinology 137:5739–5742

[42] Hughes R, Timmermans P, Schrey MP (1996) Regulation of arachidonicacid metabolism breast cancer cells by interleukin-1andphorbolester :dissociation of am ediatory role for prostaglandinE2 in the autocrine control of cell function. Int J Cancer 67:684–689

[43] Miller WR, Larionov (2010) A: Changes in expression of oestrogen regulated and proliferation genes with neo adjuvant treatment highlight heterogeneity of clinical resistance to the aromatase inhibitor, letrozole. Breast Cancer Res, 12:RS2

[44] Miller WR, White S, Dixon JM, Murray J, Renshaw L, Anderson TJ (2006): Proliferation, steroid receptors and clinical/pathological response in breast cancer treated with letrozole. Br J Cancer , 94:1051-1056.

[45] Miller WR, Larionov AA, Renshaw L, Anderson TJ, White S, Murray J, Murray E, Hampton G, Walker JR, Ho S, Krause A, Evans DB, Dixon JM(2007): Changes in breast cancer transcriptional profile les after treatment with the aromatase inhibitor, letrozole. Pharmacogenet Genomics, 17:813-826.

[46] Mackay A, Urruticoechea A, Dixon JM, Dexter T, Fenwick K, Ashworth A, Drury S, Larionov A, Young O, White S, Miller WR, Evans DB, Dowsett M (2007): Molecular response to aromatase inhibitor treatment in primary breast cancer. Breast Cancer Res, 9:R37

[47] Geisler J, Lonning PE (2001): Resistance to endocrine therapy of breast cancer: recent advances and tomorrow's challenges. Clin Breast Cancer, 1:297-308.

[48] Perey L, Paridaens R, Hawle H, Zaman K, Nolé F, Wildiers H, Fiche M, Dietrich D, Clément P, Köberle D, Goldhirsch A, Thürlimann B:(2007) Clinical benefit t of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: fi nal results of phase II Swiss Group for Clinical Cancer Research Trial (SAKK 21/00). Ann Oncol, 18:64-69

[49] Johnston S (2004): Fulvestrant and the sequential endocrine cascade for advanced breast cancer. Br J Cancer 90(Suppl 1):S15-18

[50] Lonning PE: (2009)Lack of complete cross-resistance between different aromatase inhibitors; a real finding in search for an explanation? Eur J Cancer 2009, 45:527-535

[51] Beresford M, Tumur I, Chakrabarti J, Barden J, Rao N, Makris A(2010): A qualitative systematic review of the evidence base for non-cross-resistance between steroidal and non-steroidal aromatase inhibitors in metastatic breast cancer. Clin Oncol (R Coll Radiol) , 23:209-215

[52] Miller WR: Aromatase inhibitors and breast cancer. Minerva Endocrinol (2006), 31:27-46.

[53] Lonning PE: Pharmacology of new aromatase inhibitors. Breast (1996,) 5:202-206.

[54] Miller WR, Jackson J :(2003) the therapeutic potential of aromatase inhibitors. Expert Opin Investig Drugs, 12:1-12

[55] Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J, Mauriac L, Ellis M, Lassus M, Chaudri-Ross HA, Dugan M, Borgs M(2001); Letrozole Neo-Adjuvant Breast Cancer Study Group: Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multi-centre study. Ann Oncol 2001, 12:1527-1532.

[56] Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, Apff elstaedt J, Smith R, Sleeboom HP, Jaenicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Chaudri-Ross H, Lang R, Wyld P, Bhatnagar A:(2003) Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol , 21:2101-2109.

[57] Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, Piccart MJ, Bogaerts J, Therasse P (2003): Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European organisation for research and treatment of cancer breast cancer cooperative group. Ann Oncol, 14:1391-1398

[58] Miller WR, Larionov A (2010): Changes in expression of oestrogen regulated and proliferation genes with neo adjuvant treatment highlight heterogeneity of clinical resistance to the aromatase inhibitor, letrozole. Breast Cancer Res 2010, 12:RS2

[59] Ingle JN, Johnson PA, Suman VJ, Gerstner JB, Mailliard JA, Camoriano JK, Gesme DH Jr, Loprinzi CL, Hatfi eld AK, Hartmann LC(1997) A randomized phase II trial of two dosage levels of letrozole as third-line hormonal therapy for women with metastatic breast carcinoma. Cancer , 80:218-224.

[60] Jones S, Vogel C, Arkhipov A, Fehrenbacher L, Eisenberg P, Cooper B, Honig S, Polli A, Whaley F, di Salle E, Tiff any J, Consonni A, Miller L(1999): Multicentre, Phase II trial of exemestane as third-line hormonal therapy of postmenopausal women with metastatic breast cancer. J Clin Oncol , 17:3418-3425.

[61] Rose C: A (2003) comparison of the efficacy of aromatase inhibitors in second line treatment of metastatic breast cancer. Am J Clin Oncol ; 26(suppl 1):S9-S16.

[62] Paepke S, Tulusan A, Kiesel L, Bastert G, Jaenicke FK, Bouterfa H, Wackwitz B(2003): A multi-centre study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PgR positive breast cancer. Proc Am Soc Clin Oncol : Abstract 321.

[63] Dixon JM, Renshaw L, Macaskill EJ, Young O, Murray J, Cameron D, Kerr GR, Evans DB, Miller WR (2009): Increase in response rate by prolonged treatment with neoadjuvant letrozole. Breast Cancer Res Treat, 113:145-151.

[64] Macedo LF, Guo Z, Tilghman SL, Sabnis GJ, Qiu Y & Brodie A(2006) Role of androgens on MCF-7 breast cancer cell growth and on the inhibitory effect of letrozole. Cancer Research 66 7775–7782. (https:// doi.org/10.1158/0008-5472.CAN-05-3984)

[65] Jelovac D, Sabnis G, Long BJ, Macedo L, Goloubeva OG & Brodie AM (2005)Activation of mitogen-activated protein kinase in xenografts and cells during prolonged treatment with aromatase inhibitor letrozole. Cancer Research 65 5380–5389. (https://doi. org/10.1158/0008-5472.CAN-04-4502

[66] Mayer IA, Abramson VG, Isakoff SJ, Forero A, Balko JM, Kuba MG, Sanders ME, Yap JT, Van den Abbeele AD, Li Y(2014), et al. Stand up to cancer phase Ib study of pan-phosphoinositide-3-kinase inhibitor buparlisib with letrozole in estrogen receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. Journal of Clinical Oncology 32 1202–1209. (https://doi.org/10.1200/ JCO.2013.54.0518)

[67] Blackwell K, Burris H, Gomez P, Lynn Henry N, Isakoff S, Campana F, Gao L, Jiang J, Mace S & Tolaney SM (2015)Phase I/II dose-escalation study of PI3K inhibitors pilaralisib or voxtalisib in combination with letrozole in patients with hormone-receptor-positive and HER2negative metastatic breast cancer refractory to a non-steroidal aromatase inhibitor. Breast Cancer Research and Treatment 154 287–297. (https://doi.org/10.1007/s10549-015-3615-9

[68] Hole S, Pedersen AM, Lykkesfeldt AE & Yde CW 2015b Aurora kinase A and B as new treatment targets in aromatase inhibitor-resistant breast cancer cells. Breast Cancer Research and Treatment 149 715–726. (https://doi.org/10.1007/s10549-015-3284-8)

[69] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, et al. (2014) Final results of a randomized Phase II study of PD 0332991, a cyclic-dependent kinase (CDK)-4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2-advanced breast cancer (PALOMA-1; TRIO-18). Cancer Research 74 (19 Suppl) CT101. (https:// doi.org/10.1158/1538-7445.AM2014-CT101)

[70] Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, Zirkelbach JF, Yu J, Liu Q, Zhao L, et a Bhat-Nakshatri P, Wang G, Appaiah H l Luktuke. (2015) FDA approval: palbociclib for the treatment of postmenopausal patients with estrogen receptor-positive, HER2-negative metastatic breast cancer. Clinical Cancer Research 21 4760–4766. (https://doi. org/10.1158/1078-0432.CCR-15-1185)

[71] Hole S, Pedersen AM, Lykkesfeldt AE & Yde CW 2015b Aurora kinase A and B as new treatment targets in aromatase inhibitor-resistant breast cancer cells. Breast Cancer Research and Treatment 149 715–726. (https://doi.org/10.1007/s10549-015-3284-8)

[72] Sabnis GJ, Goloubeva OG, Kazi AA, Shah P & Brodie AH (2013)a HDAC inhibitor entinostat restores responsiveness of letrozole-resistant MCF-7Ca xenografts to aromatase inhibitors through modulation of Her-2. Molecular Cancer Therapeutics 12 2804–2816. (https://doi. org/10.1158/1535-7163.MCT-13-0345)

[73] Soliman AJ, Shah P, Yu S, Sabnis GJ, Goloubeva O, Rosenblatt P, Kazi A, Chumsri S & Brodie A (2015) Histone deacetylase inhibitor entinostat in combination with a retinoid downregulates HER2 and reduces the tumor initiating cell population in aromatase inhibitor-resistanbreast cancer. Breast Cancer Research and Treatment 152 499–508. (https://doi.org/10.1007/s10549-015-3442-z)

[74] Macedo LF, Sabnis GJ, Goloubeva OG & Brodie A (2008)Combination of anastrozole with fulvestrant in the intratumoral aromatase xenograft model. Cancer Research 68 3516–3522. (https://doi.org/10.1158/00085472.CAN-07-6807)

[75] Rechoum Y, Rovito D, Iacopetta D, Barone I, Ando S, Weigel NL, O'Malley BW, Luktuke Brown PH & Fuqua SA(2014) AR collaborates with ERalpha in aromatase inhibitor-resistant breast cancer. Breast Cancer Research and Treatment 147 473–485. (https://doi.org/10.1007/ s10549-014-3082-8)

[76] Vilquin P, Villedieu M, Grisard E, Ben Larbi S, Ghayad SE, Heudel PE, Bachelot T, Corbo L, Treilleux I, Vendrell JA, et al. (2013) Molecular characterization of anastrozole resistance in breast cancer: pivotal role of the Ak /mTOR pathway in the emergence of de novo or acquired resistance and importance of combining the allosteric Akt inhibitor MK-2206 with an aromatase inhibitor. International Journal of Cancer 133 1589–1602. (https://doi.org/10.1002/ijc.28182)

[77] Schmid P, Pinder SE, Wheatley D, Macaskill J, Zammit C, Hu J, Price R, Bundred N, Hadad S, Shia A, et al. (2016) Phase II randomized preoperative window-of-opportunity study of the PI3K inhibitor pictilisib plus anastrozole compared with anastrozole alone in patients with estrogen receptor-positive breast cancer. Journal of Clinical Oncology 34 1987–1994. (https://doi.org/10.1200/ JCO.2015.63.9179)