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Review Article……!!!

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FIRST GENERATION STEROIDAL AROMATASE INHIBITOR

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ABSTRACT

Aromatase inhibitors (AIs) are a class of drugs used in the treatment of breast cancer in postmenopausal women and gynecomastia in men. They may also be used off-label to reduce increase of estrogen conversion during cycle with external testosterone. They may also be used for chemoprevention in high risk women. Aromatase is the enzyme that synthesizes estrogen. As breast and ovarian cancers require estrogen to grow, AIs are taken to either block the production of estrogen or block the action of estrogen on receptors. In this review, an endeavour has been made to emphasize aromatase inhibitors in concise manner.

INTRODUCTION

Steroidal aromatase inhibitor are class of drug that are mostly used for treating the breast cancer in postmenopausal women. The high level of the estrogen it increases the risk of breast cancer. It is classified into mainly the two types are as,

1.Non steroidal

2.steroidal

Oestrogen play an important role in development and growth of hormone dependent breast tumour. Treating breast cancer with aromatase inhibitor is only effective in postmenopausal women, because high level of aromatase ligand in overies of women.aromtase is an one type of enzyme that synthesize the estrogen. Skin, adipose tissue, muscles and malignant breast tissues are the main site of estrogen biosynthesis. It increases the estrogen synthesis with weight in postmenopausal women is most likely explanantion for increases risk of breast cancer.

In a breast and ovarian cancer require estrogen to grow ,are taken to block the action of estrogen on receptor. The anastrozole, letrozole, and exemenstane are the aromatase inhibitors. Recently the tamoxifen is non steroidal agent used in breast cancer, which act as antiestrogen.

Generally the aromatase inhibitor are classified into , first generation (e.g. aminoglutethimide), second generation (e.g. fadrazole), third generation (e.g. anastrozole and letrozole) compounds. The anti aromatase inhibitors are also classified into ,

1. Type-1 inhibitor.
2. Type-2 inhibitor.

In type-1 inhibitors have a steroidal structure, similar to androgen and inactivate the enzyme irreversibly.

In type-2 inhibitors are the non steroidal and their action is reversible.

Development of aromatase inhibitor:

The main approach of development of aromatase inhibitor is to reduced the growth stimulating effect of estrogens in breast cancer. One is the ability of estrogen to binds its receptor. And decreasing the level of estrogen.

A .Steroidal inhibitors:

1.Competitive enzyme inhibitor:

The competitive enzyme inhibitor are the molecule that compete with a substrate androsteneodione, for non-covalent binding to active site of enzyme to decrease amount of product formed. These inhibitors binds to aromtase cytochrome P450 enzyme as substrate androsteneodione several steroidal aromtase inhibitors contain the modification at c-4 position

with 4-hydroxy-androsteneodione are a prototype agent.The 4-hydroxyandrosteneodione was a competitive inhibitor.

2.Mechanism based enzyme inhibitor:

It is an inhibitor that mimics the substrate is converted by enzyme to reactive intermediate and inactivation of enzyme. A mechanism based inhibitor produced time dependent inactivation of enzyme only in presence of catalytically active enzyme. these inhibitor have distinct advantages in drug design, because these inhibitor are highly specific. They are produced a prolong inhibition and often exhibit the toxicities. The first compound designed as mechanism based inhibitors of aromtase was 10-propargyl-4-estrene-3,17-dione. These inhibitors can be grouped into general categories of 4-substituted androst-4-ene-3,17-diones, substituted androsta-1,4-dienes-3,17-diones and 6-methylene or 6-oxo-androst-4-ene-3,17-diones.

B. Non-steroidal inhibitor:

1. First and second generation inhibitor:

These generation posseses the heteroatom as common chemical features. And it interfere with steroid hydroxylations by binding of heteroatoms as common with hemeiron of cytochrome p450. Aminoglutethimide was prototype for non steroidal aromtase inhibitor. This aminoglutethimide was origenally antiepileptic agent.that was removed from market due to serious side effect. It is refered to as first generation aromtase inhibitor.

2.Third generation triazole inhibitor:

Triazole analoge is a anastrozole which is an achiral triazole derivative. The anastrozole is an potent aromtase inhibitor,with an IC 50 of 15 nm in human placental microsome. The third triazole derivative letrozole is potent inhibitor of aromtase with an IC 50 of 11.5nm in human placental microsome.

3. Flavonoid derivative as inhibitor:

Flavonoid are plant natural produce present in many food sources , including fruits, vegetables, legumes and whole grain. The flavons, isoflavons, flavanones and flavonols are possesing the benzopyranone ring system as comman chemical scaffold. Generally flavones and flavanones have higher aromtase inhiobitory activity than isoflavons. Isoflavones are significantly less potent as aromtase inhibitor.

Aromatase inhibitor in breast cancer

A. First and second generation aromatase inhibitor:

1. **Aminoglutethimide**:

The aminoglutethimide was first inhibitor are evaluated in clinical studies for for treatment of hormone dependent breast cancer. The side effects of lethargy, ataxia and morbilliform skin rash and the development of more potent aromtase inhibitor.

2.4-hydroxyandrostenedione:

4-hydroxysteneodione is a generic name of form estane was evaluated in clinical trials and was first aromtase inhibitor. The decrease the serum estrogen levels have been observed in postmenopausal breast cancer patient. 4-hydroxyandrosteneodione (formestane) was the second aromtase inhibitor to be studied in patient. It is reffered to as second generation aromtase inhibitor.

2. Third generation aromtase inhibitor:

1.Anastrozole:

Anastrozole is a non steroidal aromtase inhibitor. In this case decrease the plasma estradiol level in dose dependent manner .the anastrazole was more effective than tamoxifen (20mg daily) as first line therapy in women. The 1mg of dose daily of anastrozole is effectively suppressed total body aromatization.

2.Letrazole:

Letrazole produced approximated 99% inhibition of estrogen biosynthesis at dose 2.5 mg/d in patient. Letrazole is well tolerated cuase the decreased in serum and urine estrogen level.

3.Exemestane:

Human placental aromtase is an steroidal inhibitor of exemestane. A single oral dose of 25mg was found to cause the reduction in plasma and urinary estrogen levels.

Clinical Study

United states approved the third generation aromtase inhibitor in treatment of postmenopausal women with metastatic estrogen dependent breast cancer. The letrozole and anastrozole are more effective than tamoxifen. The tamoxifen is an first line therapy in advanced breast cancer. The exemestane has show enhance efficacy over tamoxifen. In the clinical efficacy and primary objectives of (comlete response, partial response or a disease stabilization).

Side effect

Increses risk for developing osteoporosis and joint disorders such as arthritis, arthrosis and joint pain. Also decreased rate of bone maturation and growth , infertility, aggressive behaviour, adrenal insufficiency, kidney failure, liver disfunction.

Mode of action

The aromtase inhibitor which work by the inhibiting the action of enzyme aromtase. This aromtase enzyme which convert the androgens into estrogen and this process called as aromtization. Breast tissue are stimulate the estrogens and decreased the production of breast tumor tissues. The estrogen is produced and act localy in tissues but the circulating the estrogens in men and women ,is result of estrogen escaping local metabolism.

Pharmacology of aromtase inhibitor

In postmenopausal women ovarian estrogen production diminishes with age. In these women estrogen concentration are maintain by aromtase. A cytochrome P450 enzyme complex which act final step in estrogen synthesis pathway and catalyased production of estrogen i.e estrone and esradiol. The drug act by suppression of supply of endogenous estrogen in fat, liver,and muscle cells and in breast tumor tissue.

CONCLUSION

In modern selective aromtase inhibitor it sharply represent an importanat clinical advanced for postmenopausal women with with breast cancer. The aromtase inhibitor i.e. steroidal and non steroidal agents have useful in treatment of breast cancer. These both agents are prevent the synthesis of estrogen in body. These both inhibitors have developed into very potent compound that are highly selective for aromtase vs. other steroidogenic cytochrome P450 enzyme.

REFERENCES

1. www.wikipedia.com.
2. Robert .W. Brueggemeir John c. Hackett. And Edgar.s.Diaz-cruz. The new England journal of medicine. Department of breast medical oncology M.D.Anderson cancer center, university of taxus. The royal marsden hospital and institute of cancer research London.