REVIEW ARTICLE

Review of hormonal treatment of breast cancer

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Abstract

This critical review focuses on the role of steroid hormones and their receptors in the development and treatment of breast cancer, with special reference to estrogen receptors, as well as mechanisms of receptor-ligand interactions, response or resistance to hormonal therapy against breast cancer, in conjunction with other modalities like surgery and chemotherapy. Tamoxifen is used in hormonal treatment of breast cancer for up to five years, depending on the presentation. However, there have been recent developments in hormonal therapy of breast cancer in the last ten years, with the introduction of many different alternative therapies for this condition. A critical review of published articles in Pubmed/Medline, Athens, AJOL, NHS Evidence, Science Direct and Google, relating to hormonal treatment of breast cancer, was undertaken, in order to evaluate the mechanisms of estrogen receptor-ligand interactions, their involvement in the etio-pathogenesis of breast cancer, resistance of breast cancer cells to anti-hormonal agents, as well as ways of treating breast cancer using anti-hormone drugs like tamoxifen. Although tamoxifen is the established drug for hormonal treatment of breast cancer, cases of hormone resistance breast cancer have been described recently in the literature. This can happen from the beginning, or during treatment. Therefore, we aim to examine the causes of resistance to hormonal treatment with a view to understand the options of tackling this problem, and suggest other novel alternative hormonal therapies that can be tried, which may overtake tamoxifen in the future. We also seek to emphasize that hormonal therapy has a definite place in the treatment of breast cancer along with surgery, chemotherapy and radiotherapy, as the disease is often considered to be multi-systemic even from the beginning.

Key words: Breast cancer, hormones, estrogen, progesterone

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Introduction

Breast cancer is the most common cancer worldwide, and the second leading cause of cancer death.[1] One in nine women in the UK and USA will develop the disease in their lifetimes. It is more common in Western countries, and many factors have been implicated in its etio-pathogenesis.[2] These include age, genetics, family history, diet, alcohol, obesity and physical inactivity. Others are endocrine factors (both endogenous and exogenous) mammographic density and previous benign disease.[3]

The genetic factors implicated include germ-line mutations in high-penetrance genes such as BRCA1 and 2, P_{53}, PTEN (phosphatase and tensin homologue deleted on chromosome ten), and over-expression of HER-2/neu antigen.[4] Both endogenous and exogenous steroid hormones such as estrogens and progesterone have been implicated in the pathogenesis of breast cancer due to their significant effects on cell growth, differentiation and function in the breast and other tissues.[4]

Common classes of drugs used for this purpose include the selective estrogen receptor modulators (SERMs) typified by tamoxifen,[5] selective estrogen receptor down-regulators (SERDs), represented by fulvestrant,[6] aromatase inhibitors like aminoglutethimide,[1] and leutinizing hormone releasing hormone agonists like buserelin and goserelin.[2] Tamoxifen has an established place in both prevention and treatment of

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breast cancer, but because of its side effects, new generation drugs have been introduced, but are yet to replace tamoxifen in clinical practice.[1]

Molecular Genetics of Breast Cancer

Five to ten percent of all breast cancers arise from germ-line mutations in high-penetrance breast cancer susceptibility genes such as BRCA1, BRCA2, p53 and PTEN, and confer a high individual risk for developing hereditary breast cancer.[3] The BRCA1 gene is located on the long arm of chromosome 17, while BRCA2 is located on the long arm of chromosome 13. Gene-positive patients have an 80% risk of developing breast cancer especially in the pre-menopausal age group.[4]

Aguas *et al.*,[1] observed that BRCA1 and BRCA2 predispose a woman to breast cancer in only 5-10% of the total number of breast cancers and believe that even though family history may reflect shared genes, it may also suggest shared environmental lifestyle exposures. They therefore advised that due to ethical and legal issues, as well as psychological consequences, genetic screening should only be carried out in the research settings, rather than in routine clinical practice. But we know that genetic screening is carried out selectively in affected families.

Furthermore, Russell *et al.*[4] agreed on the presence of polymorphisms in breast cancer susceptibility genes with low penetrance, which have a greater contribution to breast cancer pathogenesis in combination with exogenous factors such as diet, alcohol and pollution, as well as endogenous factors such as estrogens and progesterone exposures.

This accounts for majority of the sporadic (non-familial) breast cancers which form 90-95% of all breast cancers in women. The familial cancers usually occur in younger patients are often multi-focal or bilateral and have poorer prognosis, compared to the sporadic cases which are mostly unilateral, occurring in older patients and have better outcomes.[3]

The role of HER-2/neu antigen

This is a growth factor protein which is over-expressed in different types of human cancers, including breast, ovarian, lung, gastric, and oral cancers.[7] In 1987, the HER-2/neu proto-oncogene was revealed to be amplified and over-expressed in 20-30% of invasive breast cancers, and also shown to be associated with poorer outcome and shortened survival.[8]

In addition, HER-2/neu-positivity is thought to predict the likelihood of resistance or sensitivity to some conventional hormonal therapies like tamoxifen. Herceptin (trastuzumab), a recombinant humanized anti-HER-2/neu monoclonal antibody, has been shown to improve outcomes for women with metastatic breast cancer, either alone or in combination with chemotherapy.[9]

Recently, it has been observed that some cases of breast cancer are resistant to hormonal therapy (in spite of ER positivity) either *ab initio* or while on treatment, and several mechanisms have been postulated to explain these, and many strategies are currently being tried to overcome this resistance, including the simultaneous use of both herceptin (trastuzumab) and tamoxifen to block both the ERs and the Her-2/neu receptor, respectively. However, further investigations and clinical trials are necessary before these agents become fully established.

Steroid Hormones and their Receptors

Steroid hormones

These include estrogens, progesterone and androgens; they are manufactured from one common parent molecule, cholesterol via a reaction catalyzed by several enzymes to produce a wide variety of hormones for different target tissues and organs.[2]

Estrogens have significant effects on growth, differentiation and functioning of many tissues such as breast, uterus, cardiovascular system, brain and urogenital tract of both males and females.[2,6]

Steroid hormone receptors

These are structurally-related intra-cellular proteins that bind to steroid hormones such as estrogens and progesterone and relay their signals leading to down-stream gene expression (signal transduction). Cancers dependent on steroid hormones include breast, prostate, testicular, ovarian and endometrial cancer which result from deregulation of hormone secretion, signaling and receptor action.[10]

Estrogen receptors

Estrogen mediates its functions through two specific intra-cellular receptors estrogen receptor- α(ER-α) and β (ER-β).[2] These, along with androgen receptors (AR), are the members of the nuclear hormone receptor superfamily which form homo-dimers and bind specific DNA elements called hormone responsive elements (HRE) in the target gene promoters.[11]

In Figure 1 A demonstrates the different components of the two estrogen receptors, while B demonstrates percentage homology of the various receptor parts between ER-α and ER-β. DBD=DNA-binding domain, LBD=Ligand-binding domain, TAF 1 and 2=NLS=[2] Adapted with kind permission from Elsevier, License number 2703630992911

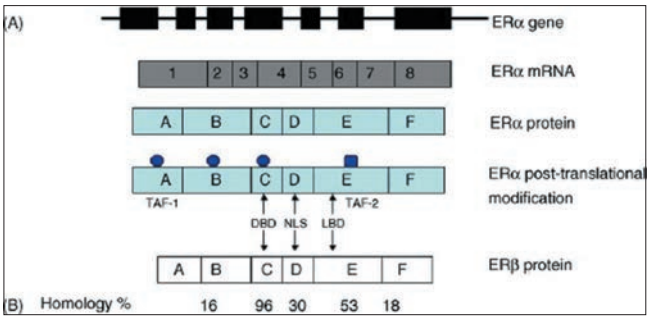

Figure 1: Organization and functional domains of estrogen receptors

Mechanism of Estrogen Receptor-Ligand Interaction

On estrogen binding, the receptors undergo a conformational change within the ligand-binding domain (LBD), which allows recruitment of co-activator proteins. Ligand-bound estrogen receptors function directly as transcription factors by binding DNA as homo-dimers to specific sequences called estrogen responsive elements (ERE), which contain short repeated sequences close to target genes. But, it has been found that about one-third of genes regulated by ERs do not contain the ERE-like sequences and that ER can regulate gene expression without binding directly to DNA by modulating the function of other transcription factors through protein-protein interactions in the nucleus.[3]

In this way, ERs may function as co-activator proteins by stabilizing DNA binding of other transcription factors or by recruiting other co-activators to these complexes. Apart from these nuclear actions of estrogens, there are some effects of estradiol which are mediated by an extra-nuclear membrane-associated ER which is transcribed from the same source as the nuclear ER. This non-genomic membrane-initiated steroid signaling occursacutely with the addition of estrogen.[12] The overall effect of this receptor-ligand interaction is to cause significant effects on growth, differentiation, and functioning of many tissues which include the mammary glands, uterus, bone, cardiovascular system, brain and urogenital tract of both sexes. Prolonged and/or excessive receptor-ligand interaction may lead to hyper-proliferation and malignant transformation especially in the breast and uterus.[4]

The estrogen receptor (ER) acts as transcription factor to promote cellular responses, but a part of cellular ER also associates with membrane in caveolae or caveolae-related lipid rafts on ligand activation. This association may be promoted by post-translational modification of the receptor. In these specialized membrane regions, ER may also interact with Her-2 (ligand-independent activated receptors), by association with adaptor proteins, such as Shc or lipid raft structural proteins. These receptors may then form a signaling complex for signal transduction to MAPK and/or AKT kinases, which communicate in turn with nuclear

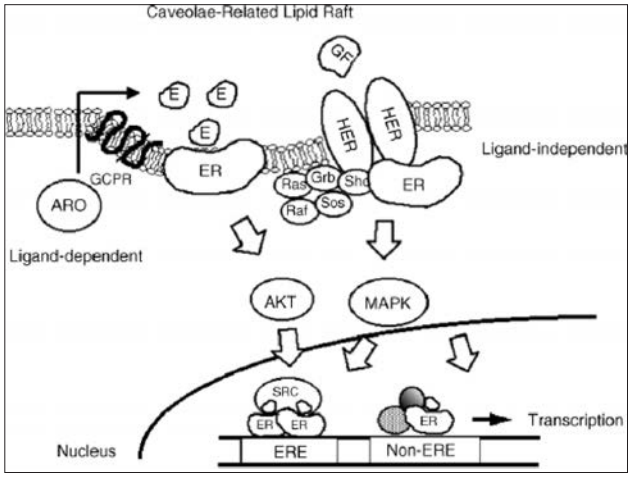

Figure 2: Interaction of growth factor receptor signaling in regulating growth of human breast cancers

ER and steroid receptor co-activator proteins (SRC) such as AIB1. Signaling for cell growth in breast cancer likely involves phosphorylation of serine and tyrosine residues in nuclear ER and/or SRC proteins [Figure 2].[2] (Adapted with kind permission from Elsevier, Licence number 2703630992911).

Detection of Hormone Receptors

The determination of estrogen receptor (ER) and progesterone receptor (PR) status has become routine in breast cancer assessment because it has prognostic and therapeutic implications. There are many techniques for this purpose, but the ligand binding assay (LBA) was initially the most commonly used method.[13] In the 1990s immunohistochemical (IHC) assays were developed for the assessment of ER/PR status because it can be used for small tumors and so assists in early diagnosis.[14] A new method called NASBA (nucleic acid sequence-based amplification) was introduced, which assesses the mRNA expression of the hormone receptors in real time.[13] Further analysis revealed a good agreement between NASBA and LBA, and revealed that ER status could be predicted using this assay with high sensitivity (72.7%) and specificity (93.5%). Lamy *et al.* therefore suggested that the method can be used in conjunction with other commonly used methods especially for small tumors.

Hormonal Therapy

A lot of research has been carried out on the mechanism of action of steroid hormone receptors, which has helped to identify potential molecular targets in cells that could be used to prevent or treat breast cancer. However, there is still on-going search for drugs with maximal benefits and minimal or absent undesirable effects.[1] In this respect, there are different therapeutic approaches for hormone-dependent breast cancer which are discussed below.

Selective Estrogen Receptor Modulators

These groups of drugs act as receptor binding competitors of estrogens and block their effects. The most common and successfully used member of this group is tamoxifen, which is a non-steroidal anti-estrogen that antagonizes the effects of estrogens and used in both prevention and treatment of breast cancer.[15]

Mechanism of Action of Selective Estrogen Receptor Modulators

These drugs serve as anti-estrogens at the molecular level by binding to the ligand binding domain (AF-2) of the estrogen receptor, and because of their different structures, they cause a conformational change in the LBD which is different from that produced by estrogens.[6] This altered conformation prevents the co-activators from binding to AF-2, blocking the trans-activation function of the receptors. The AF-1 domain remains unaffected and can cause transcriptional up-regulation of the target genes. This is thought to be responsible for the partial agonist action of SERMs.[2]

Selective Estrogen Receptor Down-Regulators

These are anti-estrogens with no agonist activity and are more potent than SERMs. One of the most widely used members is fulvestrant (ICI182780), which is a steroidal anti-estrogen.[6] Fulvestrant is more effective than tamoxifen, and has a 100-fold higher affinity to the ER, with no agonist activity in the uterus. It can completely block the stimulatory activity of both estrogens and the partial agonist activity of the SERMs.[16]

Aromatase Inhibitors

The aromatase inhibitors are superior to tamoxifen in both efficacy and toxicity, and have the potential to reduce receptor-negative tumors by synergy with COX-2 inhibitors.[1] These drugs block the production of estrogens from androgens, which is the main pathway of estrogen production in post-menopausal and non-pregnant women, as well as from other sites and tissues throughout the body.[1] Estrogen from these tissues increases the local estrogen level and facilitates the pathogenesis of breast cancer. Therefore, these drugs block the enzyme involved in estrogen biosynthesis (aromatase cytochrome P450 or estrogen synthetase), and are commonly used in post-menopausal women.[2] Aminogluthetimide was the first to be used from this group, but it is non-specific and can inhibit estrogen synthesis in many other tissues apart from the breast itself, with disastrous consequences. Second generation aromatase inhibitors (AIs) with higher potency and specificity have been introduced and include anastrozole, letozole, and exemestane. These have been tried in advanced breast cancer with promising results and it is believed that they may replace SERMs like tamoxifen which lose their potency with time.[6]

Luteinizing Hormone Releasing Hormone Agonists

Luteinizing hormone stimulates the ovaries to produce estrogen. GnRH (such as Luteinizing Hormone Releasing Hormone (LHRH) causes ovarian ablation by down-regulating its own production in the hypothalamus through a reversible reaction.[2] These drugs inhibit follicular maturation, but not folliculogenesis, and so fertility can return following their discontinuation, common examples include buserelin, goserelin, leuprolin and triptorelin.

Chemoprevention of Breast Cancer

Current breast cancer research includes the evaluation of drugs to reduce the risk of initial clinical development of cancer, and in addition to anti-estrogens commonly used in high- risk populations; other compounds have also been tried.[1]

Tamoxifen

A report of the National Survey Adjuvant Breast and Bowel project (NSABP) which ended in 1997 showed a 49% reduction in the incidence of breast cancer in women given 20 mg of tamoxifen daily for five years, and estrogen receptor-positive invasive breast cancer decreased by 66%, but there was no effect on estrogen receptor negative tumors.[5] However, it is important to weigh the risk versus benefits of chemoprevention because this drug causes bone fractures and increases the risk of endometrial cancer and thrombo-embolism.[6]

Raloxifene

This is a selective estrogen receptor modulator (SERM) that has estrogenic effects on bone and lipids and anti-estrogenic effects on the breast and uterus, and so has been approved for the treatment and prevention of post-menopausal osteoporosis.[17] It has been observed that its use for four years was associated with a 62% global reduction in breast cancer, as well as a 72% reduction in invasive breast cancer.[18,19]

Unlike tamoxifen, raloxifene is not associated with increased risk of endometrial cancer.[20,21] and this raises the possibility that it may be more useful in chemoprevention than tamoxifen.[22]

Aromatase Inhibitors

These are superior to tamoxifen in both efficacy and toxicity, and have the potential to reduce receptor negative tumors by synergy with COX-2 inhibitors.[23,24] On-going trials are still testing the efficacy of these drugs not only for adjuvant

treatment, but also for primary prevention in women with high risk of breast cancer.[24]

Statins

These drugs are used to reduce the level of cholesterol in the blood and prevent cardiovascular disease, but also have a potential use in cancer management.[25]

Non-Steroidal Anti-Inflammatory Drugs

Aspirin and other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have been linked to decreased risk of breast cancer. A significant decrease in risk for regular long-term users of aspirin (21%) and other NSAIDs (49%) has been revealed.[26] These drugs inhibit cyclo-oxygenase, the rate-limiting enzyme of prostaglandins which stimulate aromatase gene expression, enhancing local estrogen biosynthesis.[27]

Retinoids

These include vitamin A and synthetic analogues which facilitate epithelial cell proliferation, but this drug is still undergoing clinical trials.[28]

Mechanisms of Resistance to Hormonal Therapy

It has been observed that *de novo* anti-estrogen resistance occurs mainly in ER-negative/PR-negative tumors, but some studies suggest that cells can sometimes switch phenotype from ER-positive to ER-negative.[12,29] This may be as a result of population remodeling or transcriptional repression of ER expression by the tumor cells. Acquired mutations have also been noticed to result in dysfunctional forms of ER in the laboratories, but rarely observed in the clinics.[12,30]

Also, response to hormonal therapy with tamoxifen has been noticed to be of shorter duration in patients with high cyclin D1 and over-expression of this cyclin in breast cancer cells leads to acute anti-estrogen resistance.[31] In addition to that, high cyclin E expression has been associated with poor relapse-free survival in patients with endocrine therapies.[32]

Approaches to overcome hormonal resistance

Many strategies are currently being tried to overcome hormonal resistance in the treatment of breast cancer.[33] One approach is to treat patients with ER-positive and growth factor receptor-positive tumors simultaneously to block both growth factor and ER-dependent signaling pathways which are known to interact and/or synergize in promoting tumor growth.[34] Enhanced anti-tumor effects in Her-2/neu-over expressing cells with ER are found by combined treatment with antibody to Her-2/neu receptor (herceptin) and tamoxifen.[33,35] Combination of herceptin with fulvestrant is even more effective in blocking growth of breast cancer cells expressing both Her-2 and ER.[36,37]

These pre-clinical approaches are currently undergoing clinical trials.[38] Growth factor receptor tyrosine kinase inhibitors alone or in combination with anti-hormone agents can be used to treat and possibly prevent endocrine-resistant breast cancer.[39,40] *in vitro* studies have shown that the EGFR tyrosine kinase inhibitor Gefitinib (Iressa) suppresses proliferation of breast cancer cells in a dose-dependent manner.[41] Shou *et al.* observed that Gefitinib interferes with growth factor receptor and ER cross-talk and to re-establish co-repressor complexes with tamoxifen-bound ER on target gene promoters.[42]

Other inhibitors of down-stream kinases such as P_{42}/P_{44} MAP kinase or P_{38} MAP kinase that are activated with tamoxifen resistance may have utility in future.[43] The phosphatidylinositol 3-kinase (PI3K/AKT) pathway interferes with ER in breast tumors.[44] A target protein for this enzyme is the molecular target of rapamycin (mTOR), which can be suppressed using rapamycin analogues.[45] Yu *et al.*[46] have assessed a rapamycin analogue (CCI-779) in pre-clinical studies and found it to have anti-tumor efficacy. Further clinical trials in combination with aromatase inhibitors (AIs) are planned.[47]

Conclusion

The role of steroid hormones and their receptors cannot be over-emphasized in the treatment of breast cancer. Although tamoxifen is the traditional anti-estrogen agent currently established in the hormonal treatment of breast cancer, its role is increasingly becoming limited due to side effects and hormone resistance in some breast cancers. As a result, newer agents with better efficacy, no effects on the endometrial tissues, and which bypass the problems of hormone resistance are being introduced and are likely to overtake or even replace tamoxifen in the hormonal treatment of breast cancer, in the future. However, further clinical trials will have to be carried out before these novel agents can have a definite place in the routine management of breast cancer, like tamoxifen.

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