REVIEW ON TAMOXIFEN FOR THE TREATMENT OF BREAST CANCER

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Abstract

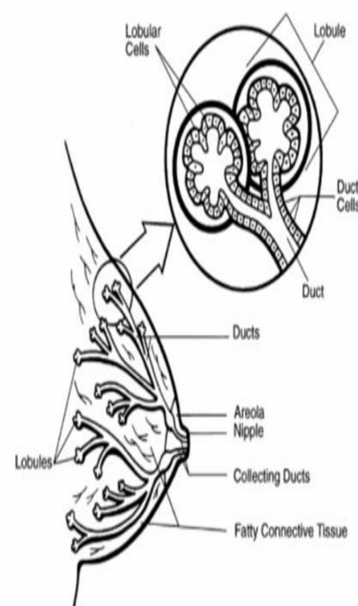
Now days, breast cancer is the most frequently diagnosed life- threatening cancer in women and leading cause of cancer death among women. Breast cancer remains one of the most prevalent cancers among women worldwide, necessitating innovative therapeutic strategies to enhance treatment efficacy and minimize side effects.Tamoxifen is a selective estrogen receptor modulator (SERM) widely used in the treatment and prevention of hormone receptor-positive breast cancer. By competitively inhibiting estrogen from binding to its receptors in breast tissue, tamoxifen effectively slows or stops the growth of estrogen-dependent tumors. Clinical studies have demonstrated that tamoxifen significantly reduces the risk of recurrence and improves overall survival rates in patients with early-stage and metastatic breast cancer. Its role as adjuvant therapy after surgery is well established, typically prescribed for a duration of 5 to 10 years based on individual risk profiles. While generally well-tolerated, tamoxifen can cause side effects, including vasomotor symptoms, mood changes, and an increased risk of thromboembolic events and endometrial cancer. Patient adherence to the treatment regimen is critical for achieving optimal outcomes, necessitating robust patient education and support. Ongoing research aims to refine its use, explore combination therapies, and investigate its potential in other malignancies. Overall, tamoxifen remains a cornerstone in breast cancer management, significantly impacting survival and quality of life for many patients.

Keywords: *Tamoxifen, Breast Cancer, Estrogen Receptor Positive, Targeted Therapy.*

Introduction:

Breast Cancer:

The breast is composed of two main types of tissues i.e., glandular tissues and stromal (supporting) tissues. Glandular tissues house the milk-producing glands (lobules) and the ducts (the milk passages) while stromal tissues include fatty and fibrous connective tissues of the breast. The breast is also made up of lymphatic tissue-immune system tissue that removes cellular fluids and waste [1].



Breast cancer is the most commonly occurring cancer in women, comprising

almost one third of all malignancies in females. It is second only to lung cancer as a cause of cancer mortality, and it is the leading cause of death for American women between the ages of 40and 55.1 The lifetime risk of a woman developing invasive breast cancer is 12.6 % 2 one out of 8 females in the United States will develop breast cancer at some point in her life.2 More than 70 year ago ,it was proposed that the breast which has never been called upon for normal function is certainly more liable to become cancerous" *[2]*and a history of breast-feeding came to be considered as a protective factor for breast cancer. This hypothesis is consistent with the pattern of geographic variation in breast cancer incidence, which is markedly lower among populations in which breast-feeding is the most common and the most prolonged *[3].*

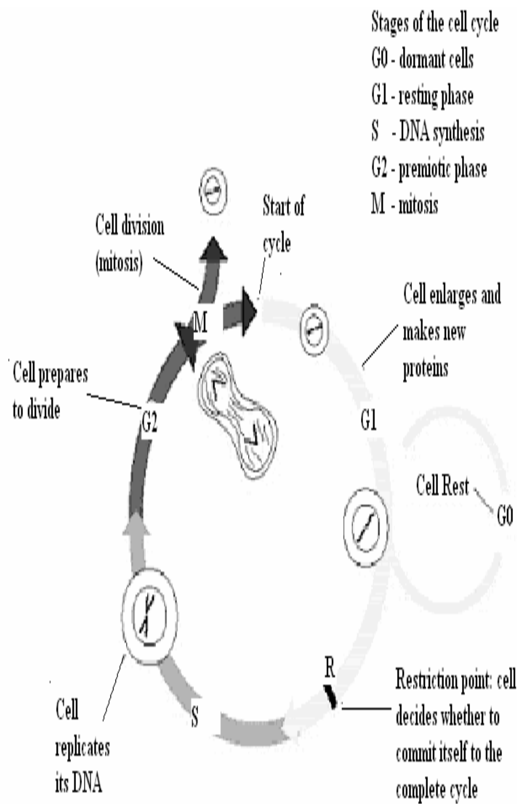
History of Breast Cancer:

- The American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography now recommend screening of women with a 20–25% or greater lifetime risk of breast cancer.
- Included in this group are women with a strong family history of breast or ovarian cancer, including those with BRCA mutation and women who received mantle radiation for Hodgkin disease between the ages of 10 and 30 years [4].
- The guidelines also state that there are several risk subgroups for which the available data are insufficient to recommend for or against screening, including women with a personal history of breast cancer.
- Among these women, tumour recurrence rates after breast conservation therapy (BCT) have historically been estimated at 1–2% per year [5].
- Recent improvements in chemotherapy and the use of tamoxifen, recurrence rates at 10 years are now less than 10%, and lifetime risk for these women depends on their age at diagnosis.
- In addition to the absolute risk of recurrence ,it is important to note that, as with the original breast cancer, the long-term survival of patients with new malignancy after BCT improves with early detection [6].
- Detection of treatment failure in these women while it is still subclinical improves relative survival by 27–47% [6].
- Conversely, large or node positive recurrent tumours' are poor prognostic indicators [7].
- The Breast Cancer Detection Demonstration Project (BCDDP) was originally sponsored by the American Cancer Society (ACS) and the National Cancer Institute(NCI).
- The BCDDP enrolled 283,222 volunteer women 35 to 74 years of age at 29 centres across the United States.
- Approximately 93,471 women were aged 40 to 49 years, 83,514 were 50 to59, and 39,471 were 60 to 69.

The cell cycle

In cancerous cells, the process of cell division is disrupted and unregulated,

Resulting in cell proliferation and tumor growth. The normal cell cycle is as Represented in figure



Types of breast cancer

According to site:

Non-Invasive Breast Cancer:

cells that are confined to the ducts and do not invade surrounding fatty and connective tissues of the breast. Ductal carcinoma in situ (DCIS) is the most common form of non-invasive breast cancer (90%). Lobular carcinoma in situ (LCIS) is less common and considered a marker for increased breast cancer risk.

Invasive Breast Cancer:

cells that break through the duct and lobular wall and invade the surrounding fatty and
connective tissues of the breast. Cancer can be invasive without being metastatic (spreading) to the lymph nodes or other organs [8].

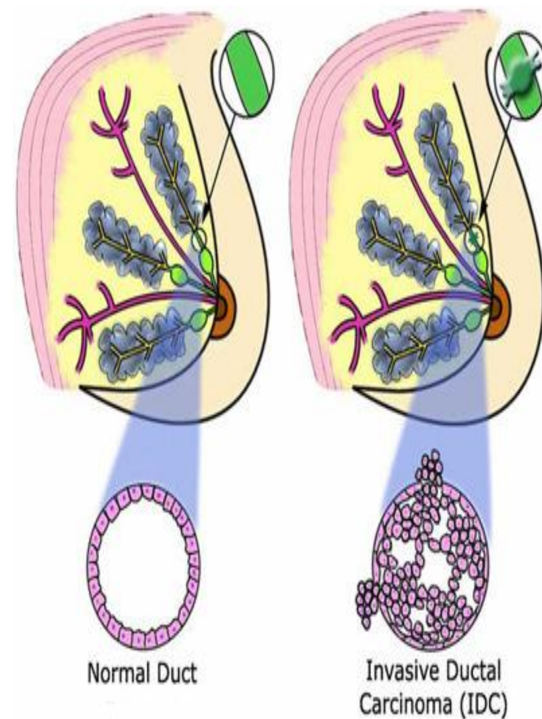
Frequently occurring Breast cancer

Lobular carcinoma in situ:

(LCIS,lobular neoplasia) The term, "in situ," refers to cancer that has not spread past the area where it initially developed. LCIS is a sharp increase in the number of cells within the milk glands (lobules) of the breast.

Ductal carcinoma in situ (DCIS):

DCIS, the most common type of non-invasive breast cancer, is confined to the ducts of the breast. For example, ductal comedocarcinoma.



Infiltrating lobular carcinoma (ILC):

ILC is also known as invasive lobular carcinoma. ILC begins in the milk glands (lobules) of the breast, but often spreads (metastasizes) to other regions of the body.

ILC accounts for 10% to 15% of breast cancers.

Infiltrating ductal carcinoma (IDC):

IDC is also known as invasive ductal carcinoma. IDC begins in the milk ducts of the breast and penetrates the wall of the duct, invading the fatty tissue of the breast and possibly other regions of the body. IDC is the most common type of breast cancer, accounting for 80% of breast cancer diagnoses [9,10].

Less commonly occurring Breast cancer

Medullary carcinoma:

Medullary carcinoma is an invasive breast cancer that forms a distinct boundary between
Tumor tissue and normal tissue. Only 5% of breast cancers are medullary carcinoma.

Mucinous carcinoma:

Also called colloid carcinoma, mucinous carcinoma is a rare breast cancer formed by the
Mucus -producing cancer cells. Women with mucinous carcinoma generally have a better prognosis than women with more common types of invasive carcinoma.

Tubular carcinoma:

Tubular carcinomas are a special type of infiltrating (invasive) breast carcinoma Women with tubular carcinoma generally have a better prognosis than women with more common types of invasive carcinoma. Tubular carcinomas account for around 2% of breast cancer diagnoses.

Causes of breast cancer

1. A previous history of breast cancer
2. Significant family history
3. Genetic causes
4. Hormonal causes
5. Life style and dietary cause
6. Environmental causes
7. Radiation Exposure
8. Reproductive history
9. Age

Sign and Symptoms

- The classic symptom for breast cancer is a lump found in the breast or armpit.
- Doing monthly breast self-exam (BSE) is a great way to be familiar with the breasts' texture, cyclical changes, size, and skin condition.
- The general alerting features of breast cancer are such as swelling or lump (mass) in the breasts welling in the armpit (lymph nodes),nipple discharge (clear or bloody), pain in the nipple, inverted (retracted) nipple, scaly or pitted skin on nipple, persistent tenderness of the breast, and unusual breast pain or discomfort.
- In Advanced stage (Metastatic) of disease underarm lymph nodes are present with other symptoms such as bone pain (bone metastases), shortness of breath (lung metastases), drop in appetite (liver metastases), unintentional weight loss (liver metastases), headaches ,neurological pain or weakness [11].

Detection of breast cancer:

As a breast cancer rarely causes pain, a pain less mass is much more worrisome for malignancy than is one causing symptoms Mammography done yearly beginning at age 40 is
the current recommendation for women with no risk factors [12].Although

mammograms may detect malignancy as small as 0.5 cm, 10% to 20% of malignancies elude detection by mammography, even when they occur at a much larger size.[13] In a patient with a solid, dominant mass (suspicious mass) the primary purpose of the mammogram is to screen the normal surrounding breast tissue and the opposite breast for non –palpable Cancers, not to make a diagnosis of the palpable mass. Thus, a negative mammogram is no guarantee of absence of malignancy, and a mass that does not disappear or Collapse with aspiration must be assumed to be a malignancy and biopsied.

Diagnosis breast cancer:

Previous studies have suggested that early breast cancer detection with suitable
Treatment could reduce breast cancer death rates significantly in the long-term [14]
Investigators have studied many diagnostic methods for diagnosing early-stage breast cancer, including mammography, MRI, ultrasonography, PET, breast MI and biopsy.

1. Mammography:

Annual mammograms are recommended by the ACS for females beginning at age 40, and they are particularly beneficial for females aged between the ages of 40 and 74 [15,16].The sensitivity could be reduced in high dense breasts and premenopausal women. Mammography has many drawbacks such as the use of ionizing radiation, and not being suitable for subjects with dense breasts, relatively high false positive and false-negative rates, and uncomfortable examination. In fact, mammography only reduced breast cancer death rates by 0.0004%, it may not be as useful as previously though[17]. CE digital mammography, which relies on tumor angiogenesis to detect breast cancer, has been recently used as an adjunct breast screening tool to mammography. It uses intravenous iodinated contrast injections and generates a slightly higher radiation compared to mammography [18].

2. Ultrasound:

Breast ultrasonography is a cost-effective and widely available screening tool, which detects
Tumors by bouncing acoustic waves off breast tissue. To identify the structure of the human breast, an ultrasound transducer is generally applied to measure the acoustic waves reflected from the breast .Breast ultrasonography increases the cancer detection rates for subjects with high breast cancer risk and it helps to identify cysts and solid masses, but less efficient compared to mammography .[19]When breast ultrasonography is performed as a supplement to mammography, it improves the sensitivity of imaging at the expense of reduced specificity and increased biopsy rates. Moreover, it requires experienced radiologists, which affects the sensitivity and specificity significantly.

3. MRI:

Creates image at different cross-sections by applying strong magnetic field with RF signals,
And contrast agent can be applied to increase the resolution of MRI image. Breast MRI has been recommended for subjects with high breast cancer risk, but it has not been recommended for the general population due to its high false-positive rate, high cost, time consumption, lack of adequate number of units, the need for

experienced radiologists and lack of clinical utility. Guidelines for MRI as an adjunct tool to mammography have been published by the ACS and annual MRI tests have been suggested for specific population groups including BRCA mutation carriers and subjects with high breast cancer risk [20].Compared to mammography and ultrasound, MRI is less specific but more sensitive to detect small tumors in subjects with high breast cancer risk

Management of Breast Cancer

Surgery:
Depending on the stage and type of the tumor, lumpectomy (removal of the lump only), or surgical removal of the entire breast (mastectomy) is performed. Standard practice requires the surgeon to establish that the tissue removed in the operation has margins clear of
Cancer, indicating that the cancer has been completely excised. Advances in sentinel lymph node mapping over the past decade have increased the accuracy of detecting sentinel lymph node from 80% using blue dye alone to between 92% and 98% using combined
Modalities [21, 22].

Radiation Therapy
Radiation therapy involves using high-energy X-rays or gamma rays that target a tumor or post-surgery tumor site. These radiations are very effective in killing cancer cells that may remain after surgery or recur where the tumor was removed.[23,24].

Chemotherapy
Chemotherapy is the use of anti-cancer drugs to treat cancerous cells. Specific Treatment for the breast cancer will be based on; overall health, medical history, age (whether menstruation is there or not), type and stage of the cancer, tolerance for specific
Medications and procedures etc. [25,26].

Nanotechnology in breast cancer
The field of nanotechnology has rapidly evolved as evidenced by the fact that there are more than 150 ongoing clinical trials investigating the efficacy of nanotechnology based drug delivery carriers targeting cancer. Various liposomal doxorubicin formulations were developed in an effort to improve the therapeutic index Nanotechnology in breast cancer
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Gene Therapy
It is generally accepted that cancer arises because of an accumulation of multiple molecular genetic defects that culminate in a cellular phenotype characterized by unregulated growth.
Based on the knowledge, a variety of gene therapy strategies have been developed as potential new therapies for cancer [28].

DRUG PROFILE:

Generic Name: Tamoxifen

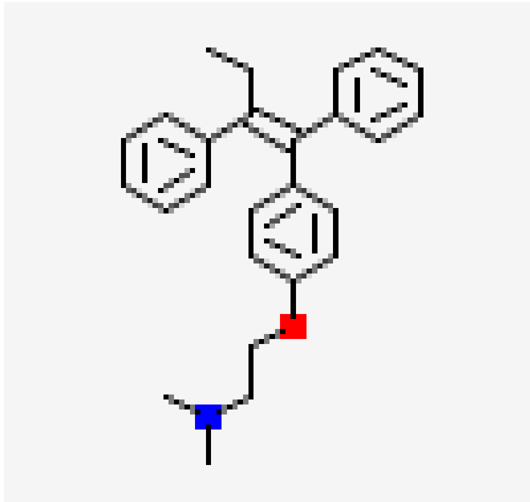
Brand Names: Nolvadex, Soltamox

IUPAC Names: (Z)-1-[4-(2-(Dimethylamino)ethoxy)phenyl]-2-phenylbut-1-ene

Class: Selective Estrogen Receptor Modulator (SERM)

Chemical Formula: $C_{18}H_{11}NO_1$

Structure of Tamoxifen:



Solubility of tamoxifen :

Water: Tamoxifen has low solubility in water, typically around 0.1 mg/mL at room temperature.

Organic Solvents: It is more soluble in organic solvents such as:

Ethanol, Methanol, Dimethyl sulfoxide (DMSO), Acetone

Implications: Due to its low water solubility, tamoxifen is often formulated in a way that enhances its bioavailability, such as using it in tablet or liquid form for oral administration.

Indications:

Breast Cancer: Tamoxifen is primarily used for the treatment of estrogen receptor-positive (ER+) breast cancer in both premenopausal and postmenopausal women. It is often prescribed for:

1. Treatment of early-stage breast cancer

2. Treatment of metastatic breast cancer

3. Reducing the risk of breast cancer in high-risk patients

Mechanism of Action:

Tamoxifen works by binding to estrogen receptors on cancer cells, thereby blocking the effects of estrogen , which can fuel the growth of certain types of breast tumors. It may also have partial agonist effects in some tissues, which can lead to varying responses depending on the location.

Pharmacokinetics:

- **Absorption:** Well-absorbed from the gastrointestinal tract.
- **Distribution:** Highly protein-bound; extensive tissue distribution.
- **Metabolism:** Primarily metabolized in the liver by cytochrome P450 enzymes (CYP2D6 and CYP3A4). Its active metabolites include 4-hydroxytamoxifen, which is more potent.
- **Excretion:** Mainly excreted in urine as metabolites.
- **Half-life:** Approximately 5 to 7 days, but its active metabolites can have a longer half-life.

Dosing:

- The typical oral dosage is 20 mg per day, but it can vary based on specific clinical scenarios and guidelines.

Side Effects:

- Common side effects include:
  - Hot flashes
  - Vaginal discharge or bleeding
  - Nausea
  - Fatigue
  - Mood swings

Serious side effects may include:

- Risk of blood clots (thromboembolic events)
- Endometrial cancer (due to estrogenic effects on the uterus)
- Stroke

Contraindications:

- History of thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism)
- Known hypersensitivity to tamoxifen or its component
- Pregnancy and breastfeeding (unless benefits outweigh risks)

Drug Interactions:

- Tamoxifen's metabolism can be affected by other medications that induce or inhibit CYP450 enzymes. Notable interactions include:
  - Antidepressants (e.g., SSRIs like paroxetine can inhibit CYP2D6)
  - Certain antifungals and antibiotics

Monitoring:

- Regular follow-ups are essential to monitor for side effects and assess the response to treatment.
- Periodic gynecological examinations due to the increased risk of endometrial changes.

Conclusion:

Tamoxifen remains a cornerstone in the management of hormone receptor-positive breast cancer. Its ability to reduce recurrence and improve survival makes it an essential component of breast cancer treatment regimens. However, careful consideration of potential side effects and patient-specific factors is vital for optimizing treatment outcomes. Ongoing research continues to refine its use, potentially incorporating it into combination therapies or exploring its role in other cancer types. Overall, tamoxifen has significantly impacted breast cancer care, contributing to improved survival and quality of life for many patients. tamoxifen is a vital component in the management of hormone receptor-positive breast cancer. Its proven efficacy in reducing recurrence and improving survival, coupled with a relatively manageable side effect profile, makes it an essential therapy. Ongoing research continues to enhance our understanding and application of tamoxifen, reinforcing its role in improving outcomes for breast cancer patients.

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