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THE RAPEUTIC ROLE OF BREAST CANCER

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ABSTRACT

Breast cancer is the most frequently diagnosed malignancy in women and remains a leading cause of cancer-related mortality worldwide. Its heterogeneity, encompassing molecular subtypes such as luminal-A, luminal-B, HER2-positive, and triple-negative breast cancer (TNBC), necessitates diverse therapeutic approaches. Advances in medicinal chemistry have played a central role in developing targeted agents that disrupt key signaling pathways, modulate hormone activity, or directly damage tumor DNA. Hormonal therapies such as aromatase inhibitors (anastrozole, letrozole, exemestane) and estrogen receptor modulators or degraders (tamoxifen, fulvestrant) act by suppressing estrogen biosynthesis or antagonizing estrogen receptor activity. Chemotherapeutic agents, including alkylating agents (cyclophosphamide) and anthracyclines (doxorubicin), exert cytotoxicity through DNA alkylation, intercalation, or free radical formation. Targeted biologics such as trastuzumab exploit HER2 overexpression by binding to its extracellular domain, and inducing antibody-dependent cytotoxicity. In TNBC, where targeted options are limited, checkpoint inhibitors such as Pembrolizumab modulate PD-1/PD-L1 signaling to restore T-cell activity. Antimetabolites like methotrexate inhibit folate-dependent enzymes crucial for DNA synthesis, while synthetic progestins such as megestrol acetate act on hormonal pathways and appetite regulation. Pharmacokinetic optimization-ensuring bioavailability, selective receptor affinity, and controlled clearance remain integral to improving therapeutic index and minimizing toxicity. Despite these advances, drug resistance, adverse effects, and limited efficacy in aggressive subtypes highlight ongoing challenges. Future directions in medicinal chemistry focus on cancer stem cell targeting, antibody-drug conjugates, and personalized therapy guided by genomic profiling. Collectively, multidisciplinary integration of pharmacology, molecular biology, and chemistry continues to drive innovation in breast cancer management.

KEYWORDS:

- Breast cancer
- Breast cancer epidemiology
- Pathophysiology
- Hormonal therapy
- Chemotherapy agent
- Targeted therapy

INTRODUCTION

Breast cancer (BC) is the most frequent malignant tumor in women and among all cancers. It has a global impact. According to an American cancer society report, breast cancer is second only to lung cancer in terms of cancer-related deaths among women. In recent years, the incidence of BC has increased at an annual rate of approximately 0.3%, with 2.3 million new cases predicted to be diagnosed worldwide by 2020. In addition, the death rate grew considerably between 1990 and 2015. The five-year survival rate for individuals diagnosed with stage IIIA and stage IIIB BC was 52% and 48%, respectively according to data from surveillance, epidemiology and end results.

The median survival rate for individuals with stage III breast cancer was 4.9 years. BC is a heterogeneous disease with a wide range of genomic traits as well as distinct biological and clinical properties. Basal-like BC, human epidermal growth factor receptor 2 (HER 2) – positive, luminal B, and luminal A, are the four main groups used to classify BC based on molecular features. Luminal A and B cancers express hormone receptors (estrogen and progesterone); but, when compared to luminal A, luminal B cancer expresses more of the cellular proliferation biomarker ki67, which is associated with a poor prognosis. The two BC drug classes that are prescribed more often than any other are aromatase inhibitors and tamoxifen and other estrogen antagonists. BC with the HER2 positive subtype, which also lacks functional estrogen and progesterone receptors, is characterized by over expression of HER2. The most popular treatment for this subtype of BC involves targeting HER2 with certain antibodies, such as trastuzumab. The lack of HER2 proteins and hormone receptors is a characteristic of basal-like BC, sometimes referred to as triple-negative BC or TNBC. Many people believe it to be the most deadly type of BC. Patients with TNBC currently have few therapy options. Despite substantial advancements in therapeutic approaches, about 30% of patients diagnosed with primary breast cancer may progress to metastatic illness. Furthermore, the 5-year survival rate for metastatic breast cancer is less than 30%. Despite

the availability of a wide range of diagnostic and treatment techniques, their efficiency and performance remain insufficient to meet all of patients' expectations, raising concerns about their viability. The effectiveness is significantly dependent, first and foremost, on the type of substance selected and subsequently administered in line with the suitable modalities.

Epidemiology:

The incidence of AF (atrial fibrillation) is substantially higher in breast cancer patients. A major epidemiology study involving 85,423 breast cancer patients discovered that breast cancer is an independent risk factor for the development of AF. Within the first year after a breast cancer diagnosis the incidence of AF among these individuals was 3.9%, compared to 1.8% in a non-cancer control group. Further investigation indicated a strong link between breast cancer stage and the orccurence of AF, with advanced-stage patients having a more than three-fold higher chance of developing AF than those with early-stage breast cancer. Furthermore, the study discovered that some breast cancer treatment options are linked to an increased incidence of AF.

Breast cancer is not only the most commonly diagnosed cancer in women, but it is also the leading cause of female cancer fatalities world-wide, in 2020, it was responsible for roughly 685,000 fatalities world-wide, translating to an age-standardized rate of 13.6 for 100,000 women. Although industrialized countries have the greatest incidence rates, Asia and Africa accounted for 63% of breast cancer fatalities that year. Survival rates vary greatly depending on geography and economic context: women diagnosed in high-income nations typically have better results, whereas inadequate access to early identification and appropriate treatment leads to lower survival rates in many low-and middle-income locations.

The death rate for breast cancer has like-wise changed over the last few decades. From the 1970's to the 1980's, most countries motility rates progressively increased. After peaking in the late 1980's, the death rate fell dramatically as the management of breast cancer evolved. During this time period, both mass mammography screening and better therapy helped to reduce mortality. However in recent years, the drop in mortality has slowed to 1.3%, possibly due to the progressive increase in the incidence of breast cancer and the stable prevalence of screening. According to the most recent global figures, breast cancer is the top cause of cancer-related mortality in women, ranking 5th overall. By 2030, the mortality rate from lung cancer in women is predicted to surpass that of breast cancer in certain wealthy countries.

Patho-physiology:

Breast tumors typically arise from ductal hyperproliferation and, under persistent exposure to carcinogenic factors, may progress into bengin lesions or invasive metastatic carcinomas. The tumor microenvironment-particularly stromal components and macrophage activity – plays a central role in breast cancer initiation and progression. Experimental studies in rat mammary glands have shown that alterations confined to the stromal tissue, even without direct involvement of the extra-cellular matrix or epithelium can drive neoplastic transformation. Macrophages further contribute by creating a pro-inflammatory and mutagenic milieu, supporting angiogenesis, and enabling tumor cells to immune surveillance. Epigenetic modifications, such as distinct DNA methylation patterns between normal and tumor-associated tissues, also indicate that the microenvironment can actively promote carcinogenesis.

A distinct subset of malignant cells, non as cancer stem cells (CSCs), has been identified and linked to tumor initiation, metastasis, and recurrence. These cells, thought to originate primarily from luminal epithelial progenitors rather than basal stem cells, exhibit self-renewal capacity and resistance to conventional therapies such as chemotherapy and radiotherapy. The pioneering work of AI-Hajj and colleagues demonstrated that as few as 100 breast CSCs (bCSCs) were sufficient to initiate tumor formation in immunodeficient mice. The growth, survival, and invasive potential of bCSCs are regulated by key signaling pathways, including Wnt, Notch, Hedgehog, PI3K, P53, and HLF. Continued research is necessary to clarify the biology of bCSCs and to design targeted therapies capable of eradicating them.

Two major conceptual frameworks have been proposed to explain breast cancer development and progression: the cancer stem cell hypothesis and the stochastic theory. The CSC model suggests that tumors arise from stem or progenitor cells, with hetero-geneity resulting from genetic and epigenetic alterations acquired during tumor evolution. In contrast, the stochastic model posits that any breast cell can become malignant after accumulating sufficient random mutations, with each tumor subtype derived from a distinct transformed cell type. Both models are supported by substantial evidence; however, neither fully captures the complete etiology of breast cancer.

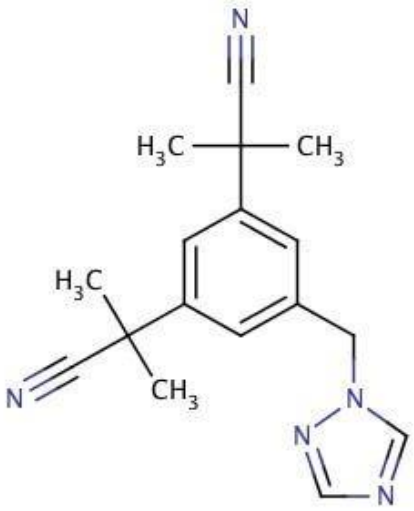
Drugs used to treat in breast cancer:

1. Hormonal therapies

Anastrozole:

Anastrozole is a non-steroidal aromatase inhibitior (AI) that, like letrozole, is used to lower circulating estrogen levels in postmenopausal women with estrogen-responsive breast cancer. Anastrozole is similar to exemestane, a steroidal AI, but its non-steroidal nature offers significant advantages, including the absence of steroid-related side effects such as weight gain and acne. Aromatase inhibitors, particularly anastrozole, have become the preferred endocrine medications in the treatment of postmenopausal breast cancer due to their superior efficacy and side effect profile hen compared to older estrogen receptor modulators such as tamoxifen. Anastrozole was initially licensed for usage in the United States in 1995.

Structure:



Mechanism of action:

Anastrozole works against estrogen by selectively and competitively inhibiting the aromatase enzyme, which is located mostly in the adrenal glands, liver, and fatty tissues. Many breast tumors are hormone receptor-positive, which means that hormones like estrogen and progesterone encourage and/or maintain their growth. In postmenopausal women, estrogen is primarily derived from the aromatase enzyme's conversion of adrenally produced androgens into estrogens; by competitively inhibiting estrogen biosynthesis at these enzymes, anastrozole effectively suppresses circulating estrogen levels and, as a result the growth of hormone receptor-positive tumors.

Pharmacokinetics:

Across a dosing range of 1-20 mg, anastrozole demonstrates linear pharmacokinetic with minimal variabililty both between and within patients. At the standard daily dose of 1mg, the drug achieves its maximum plasma concentration (Cmax = 13.7 L) approximately two hours after administration. Absorption occurs more quickly in fasting women, although food does not affect the overall extent of absorption. When administered at doses between 0.5 and 10mg daily to postmenopausal women or patients, steady-state plasma levels are reached within 9-10 days and are about three higher than those seen after a single dose. Anastrozole is predominantly metabolized in the liver through N-dealkylation, glucuronidation, and hydroxylation, resulting in a terminal half-life of around 50 hours. Within 72 hours of dosing, less than 10% of the drug is eliminated unchanged in urine, whereas about 60% is excreted as metabolites. Importantly, its main metabolites-triazole, hydroxy-anastrozole, and anastrozole-glucoronide—lack aromatase-inhibiting activity. Although hepatic metabolism accounts for nearly 85% of drug clearance, patients with mild to moderate liver impairment display plasma levels comparable to those with normal liver function. Similarly because renal clearance is not a key elimination pathway, patient with renal impairment maintain normal systemic clearance and can safely receive anastrozole.

Contraindications:

- Aromatase inhibitors are not suggested for patients who have a history of hypersensitivity to these medicines; as such reactions can include anaphylaxis, angioedema, or urticaria.
- Pregnancy and postmenopausal women: aromatase inhibitors can harm the fetus or cause pregnancy loss. Because of their method of action, AIs provide no therapeutic benefit to premenopausal breast cancer patients.

Adverse effects:

Rare adverse effects (seen in <1 in 10,000 patients):

- Skin changes such as ulcers and blisters.
- Severe allergic reactions resulting in swelling of the face, lips, tongue, or throat which may cause difficulty with swallowing and breathing.
- Abnormal liver function due to inflammation, sometimes accompanied by jaundice.
- Bone loss associated with long-term estrogen deficiency.

Common adverse effects (~10% incidence):

- Hot flashes

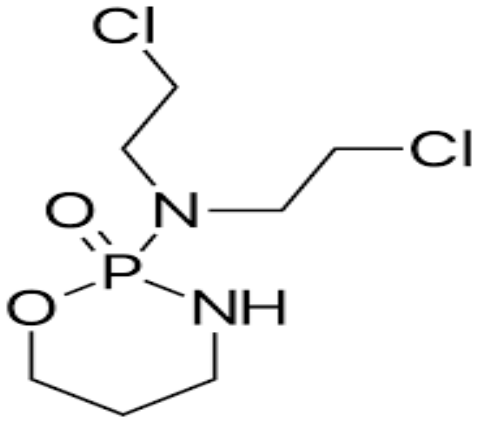
- Fatigue
- Joint- related problems such as arthritis and arthralgia
- Sexual dysfunction
- Osteoporosis and increased fracture risk

2. Chemotherapy

Alkylating agent: Cyclophosphamide

Cyclophosphamide is widely used in treating several cancers, such as breast cancer, sarcoma, and multiple myeloma. As a nitrogen mustard derivative, it works by Alkylating DNA to exert its anticancer effects. This review outlines its therapeutic indications, contraindications, mechanism of action, and other essential clinical considerations, highlighting its role in cancer management within an interprofessional care team. Additionally, the use of cyclophosphamide in severe cases of multiple sclerosis is also discussed.

Structure:



Mechanism of action:

Cyclophosphamide is a nitrogen mustard derivative that acts through DNA alkylation. It is not specific to any cell-cycle phase and is metabolized into an active form capable of disrupting protein synthesis by creating cross-links in DNA and RNA. The drug's principal antitumor activity comes from its metabolite, phosphoramide mustard which is generated after hepatic metabolism by cytochrome P-450 enzymes. Initially, cyclophosphamide is converted into hydroxycyclophosphamide and then into aldophosphamide. Aldophosphamide is subsequently cleaved into phosphoramide mustard and acrolein. Phosphoramide mustard cross-links DNA at the guanine N-7 site, producing irreversible modifications that lead to apoptosis. Acrolein, through lacking antineoplastic properties, is chiefly responsible for

hemorrhagic cystitis. Beyond its Cytotoxic and antitumor actions, cyclophosphamide also exhibits immunosuppressive properties with a degree of selectively toward T cells. At high doses, it is employed to eradicate malignant hematopoietic cells, while at lower doses it is effective in modulating regulatory T cells. It reduces the secretion of interferon-gamma and IL-12 while enhancing the release of Th2 cytokines such as IL-4 and IL-10 in both the peripheral blood and cerebrospinal fluid. Owing to these effects, cyclophosphamide plays a role in tumor vaccine strategies, control of post-transplant alloreactivity, and the treatment of immune-mediated disorders and certain vasculitides. Although the exact mechanisms behind its immunomodulatory activity are not fully understood, proposed explanations include depletion of regulatory T cells in both normal and malignant hosts, stimulation of T cell growth factors like type I interferons, and priming of host cells to accept donor T cells with reduced alloreactivity.

Pharmacokinetics:

Cyclophosphamide is well absorbed orally, with peak plasma levels occurring about one hour after administration. Its apparent volume of administration is between 30 and 50L, with approximately 20% of the parent drug bound to plasma proteins, while some metabolites bind at levels exceeding 60%. The drug undergoes hepatic metabolism primarily through cytochrome P450 enzymes, including CYP2A6, CYP2B6, CYP3A4, CYP32A5, CYP2C9, CYP2B6 exhibits the greatest activity in catalyzing 4-hydroxylation. This biotransformation produces the active metabolites phosphoramide mustard (responsible for antitumor effects) and acrolein (associated with toxicity such as hemorrhagic cystitis). Cyclophosphamide is also known to induce its own metabolism with repeated dosing, which increases clearance, accelerates the generation of hydroxylated metabolites, and shortens its half-life.

Contraindications:

- Cyclophosphamide, like other Alkylating agents, is teratogenic and is contraindicated during pregnancy (category D), except when the mother's condition is life-threatening. It is also relatively contraindicated in patients who are breastfeeding or have active infections, neutropenia, or bladder toxicity.
- As a pregnancy category D drug, cyclophosphamide is associated with congenital malformations. Exposure during the first trimester whether for cancer or lupus treatment, can result in a characteristic pattern of defects referred to as "cyclophosphamide embryopathy,"

which includes growth retardation, craniofacial and ear abnormalities, absence of digits, and underdeveloped limbs.

Adverse effects:

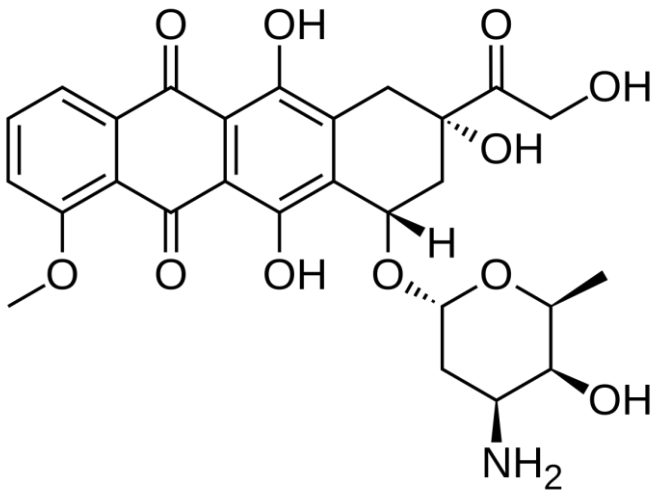
- Menstrual cycle changes
- Decrease of white blood cells, red blood cells and platelets
- Taste changes
- Bladder irritation
- Nasal congestion

3. Targeted therapy:

Trastuzumab:

Trastuzumab is an approved therapy for HER2-positive cancers, including metastatic breast cancer, adjuvant treatment of localized HER2-positive breast cancer, and metastatic adenocarcinoma of the stomach or gastroesophageal junction. In both the United States and the European Union (EU), its use is restricted to patients whose tumors demonstrate HER2 gene amplification or HER2 protein overexpression. These alterations are linked to a poorer prognosis, with reduced overall survival and shorter disease-free survival rates.

Structure:



Mechanism of action:

Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) by binding to its extracellular domain. This interaction blocks HER2 homodimerization and thereby inhibits HER2-driven signaling pathways. Additionally,

trastuzumab is believed to trigger antibody-dependent cellular cytotoxicity, resulting in the elimination of HER2-positive cells.

Antibody-drug conjugates (ADCs) represent a class of therapeutic agents that deliver Cytotoxic drugs specifically to cells expressing a target protein. Trastuzumab deruxtecan (t-DXd) is a third-generation ADC composed of a humanized anti-HER2 antibody (trastuzumab) conjugated to a topoisomerase I inhibitor (DXd) through a cleavable tetrapeptide linker. Notably, T-DXd features a high drug-to-antibody ratio of approximately 8:1. In contrast, trastuzumab emtansine (T-DM1) is a second-generation ADC in which trastuzumab is coupled to the cytotoxic agent emtansine.

Pharmacokinetics:

Absorption: When administered with hyaluronidase, trastuzumab shows improved subcutaneous absorption. Steady-state peak and trough plasma concentrations are generally reached between weeks 16 and 32.

Distribution: The apparent volume o distribution for trastuzumab is approximately 44 mL/kg, comparable to serum volume. Its ability to cross the blood-brain barrier or enter the cerebrospinal fluid has not been clearly established.

Metabolism: After binding to HER2, trastuzumab undergoes intracellular degradation into peptides and amino acids. Its elimination is believed to occur primarily through IgG clearance mediated by the reticuloendothelial system.

Elimination: Trastuzumab demonstrates nonlinear, dose-dependent kinetics. Renal excretion is minimal. The estimated half-life is about 28days, which can be prolonged in patients with higher tumor burden. Considerable interpatient variability in clearance exists, with increased body weight and reduced serum albumin levels associated with higher drug clearance rates.

Contraindications:

Pulmonary toxicity: Serious and potentially fatal pulmonary complications have been linked to trastuzumab therapy. These include interstitial pneumonitis, pleural effusions, acute respiratory distress syndrome, non-cardiogenic pulmonary edema, and pulmonary fibrosis. Such events may develop as part of infusion-related reactions. Patients with previous lung disease or pulmonary malignancies are at increased risk of experiencing severe toxic effects.

Embryo-fetal toxicity: Exposure to trastuzumab during pregnancy may lead to oligohydramnios, which carries the risk of life-threatening pulmonary hypoplasia, skeletal malformations, and neonatal death. Women of childbearing potential should undergo

pregnancy testing before starting treatment, and effective contraception is recommended during therapy and for 7 month after the final dose.

Neutropenia: When combined with myelosuppresive chemotherapy, trastuzumab may exacerbate chemotherapy-induced neutropenia. Reports of grade 3-4 neutropenia and febrile neutropenia are more frequent in patients receiving combination regimens.

Adverse effects:

Cardiotoxicity: Trastuzumab is associated with cardiotoxicity, most often seen as decline in left ventricular ejection fraction (LVEF).

Infusion-related reactions: Patients should be closely monitored for symptoms like dyspnea, hypotension, or angioedema. In select cases, re-administration is possible with pre-medication (example: acetaminophen and diphenhydramine).

Renal toxicity: Rare reports of nephritic syndrome exist, most frequently documented in patients treated for metastatic gastric cancer.

CONCLUSION:

Breast cancer remains one of the most prevalent and life-threatening malignancies among women worldwide. Despite advances in diagnostic methods, staging systems, and therapeutic strategies-including surgery, chemotherapy, hormonal therapy, targeted therapy, and immunotherapy-the disease continues to present major challenges due to its heterogeneity and high metastatic potential. Early detection through screening methods such as mammography significantly improves survival outcomes, while molecular classification helps guide personalized treatment approaches. Drugs such as aromatase inhibitors, tamoxifen, fulvestrant, trastuzumab, cyclophosphamide, doxorubicin, methotrexate and newer immunotherapeutics have expanded treatment options, but adverse effects and resistance remain barriers to long-term efficacy. Triple-negative breast cancer, in particular, continues to pose the greatest therapeutic challenge due to limited targeted options and poor prognosis.

Overall, continued research into cancer stem cells, tumor microenvironment interactions, and precision medicine is essential for developing safer and more effective treatments. Improving global access to early detection and advanced therapies, especially in low-and middle-income countries, will be critical in reducing mortality and improving quality of life for breast cancer patients.

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