BREAST CANCER OPPORTUNITIES AND CHALLENGES

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ABSTRACT:
Cancer is caused by the uncontrolled growth of abnormal cells in the body, which is influenced by genetic and environmental factors. Some of the main factors that increase the risk of breast cancer are modern lifestyle changes, food choices, genetic vulnerability, family history, oestrogen exposure, age, late night working, hazardous chemical exposure, obesity in the postmenopausal phase, and exposure to high doses of radiation. It is the most commonly diagnosed cancer and the leading cause of cancer deaths in women worldwide. Treatment and prevention of breast cancer are important issues in public health and medical practice. The current treatment strategy for this disease focuses on early detection and treatment. A literature study compiles and contrasts information on the clinical stages of breast cancer, wait times for treatment, and hurdles to access in various nations. It shows that while most high-income nations diagnose more than 70% of breast cancer patients in stages I and II, most low- and middle-income countries only diagnose 20% to 50% of patients in these earlier stages. New therapeutic approaches for breast cancer have been made possible by recent advancements in our understanding of the molecular and genetic changes underlying breast cancer's progression and development. According to the hypothesis, the result of novel treatment for breast cancer will emerge from identifying specific molecular targets that are exposed in research designed to illuminate the gene and molecules implicated in breast carcinogenesis. The fundamentals, pathophysiology, and classification of breast cancer are highlighted in this review, along with problems like multidrug resistance (by ABC transporter, P-glycoprotein, MDR-associated Protein (MRP1), breast cancer resistance protein (BCRP), drug resistance in breast cancer, and multidrug resistance in breast cancer cells in vitro), altered microtubules, altered enzyme, p-53 tumour suppressor gene, cell cycle, altered DNA repair processes, cell death response, and different types of It also covers potential and cutting-edge imaging methods for the treatment of breast cancer.

KEYWORDS
Breast cancer, multidrug resistance (MDR), therapeutics, imaging techniques, Chemotherapy

1. INTRODUCTION:
Breast cancer is the most common cancer in adult females worldwide (140 of 180 countries) [1], and it is the second leading cause of cancer death after lung cancer [2]. In the UK, the disease affects one in every eight women and one in every twenty in India. Breast cancer has an age-standardized incidence rate (ASR) of 39.0 per 100,000, which is higher than cervical cancer (ASR=15.2 per 100,000) [3, 4]. In the United States in 2015, an estimated 60,290 in situ breast cancer cases and 2, 31,240 invasive breast cancer cases were diagnosed. Breast cancer is expected to kill approximately 40,290 women. There are currently 3.1 million breast cancer survivors in the United States [5]. It is estimated that 70% of breast cancers are hormone receptor-positive, and genetic mutations such as the BRCA 1 and BRCA 2 genes increase the risk of developing breast cancer by 60-80% over a lifetime [6-8]. It is more prevalent in Western countries than South America, Asia, or Africa. Its pathogenesis has been linked to several aetiological factors.

Age, genetics, family history, diet, alcohol, obesity, lifestyle, physical inactivity, chemical exposure, previous benign disease, mammographic density, and exposure to high doses of ionizing radiation are all risk factors. Each factor plays a distinct role in the pathogenesis of breast cancer, making it difficult to predict which factor is more likely to cause the disease. This cancer is seen in one-fourth of all female cancers in most areas, indicating that it is most common in Western countries and a rapidly growing cancer in Asian countries [2,5]. Breast cancer is a tumour that develops from cells in the breast tissue, precisely the ducts and lobules, where most cases of breast cancer begin.
II. PATHOPHYSIOLOGY OF BREAST CANCER

The exact cause of breast cancer is still unknown. Nonetheless, numerous attempts have been made to describe the onset and course of breast cancer using molecular imagery. The cancer cell stem model, in which precursor cancer cells initiate and sustain progression, and the clonal evolution model, in which mutation accumulates, epigenetic changes in tumour cells occur, and the survival of "fittest" cells, are both implicated. In addition, the cancer stem cells may also evolve in a clonal manner [9]. From healthy glands to cancer, there are many different lesions and genetic changes at the morphological level. There is evidence that breast cancer develops along two molecularly different molecular pathways of progression, namely tumour grade and proliferation and ER expression. Also, some sporadic and inherited breast cancer diagnosis elements have been clarified by discovering breast cancer liability genes.

The first molecular pathway is the low-grade-like pathway, recognized by gain 1q, loss 16, uncommon amplification of 17q12, and a gene expression profile (GES) with a preponderance of genes linked to ER characteristics, diploid or nearly diploid karyotypes, and low tumour grade. This pathway contributes to breast cancer of the luminal A and luminal B subtypes. The second pathway, known as the high-grade-like pathway, is characterized by the loss of 13q, the gain of the chromosomal region 11q13, the amplification of the gene-encoding region 17q12 (ERBB2, which codes for HER2), and an expression profile of genes involved in cell cycle and proliferation [10].

III. CLASSIFICATION OF BREAST CANCER

Several reports recognized the complexity and heterogeneity of breast cancer. The subdivision of primary breast cancer into distinct subtypes varies in terms of diagnosis and treatment [11].

Pathologists commonly make such changes by sub-classifying tumours based on tumour stage (size, invasiveness, and metastatic status), grade (differentiation state), origin (ductal or lobular), and immunohistochemical staining. Immunohistochemical staining for progesterone receptor (PR), oestrogen receptor (ER), and human epidermal growth factor receptor (HER2) levels is standard. A year ago, advancements in technology enabled the development of a new tool for cancer research: expression array analysis. Breast tumour microarray expression profiling revealed that tumour subtypes could be distinguished based on their gene expression profiles. Normal breast-like, basal, luminal A, luminal B, and HER2/ERBB2 amplified/overexpressing breast cancers are among the various molecular subtypes [12].

For breast cancer treatment, various classes of therapeutic agents are used:

- a. Cyclophosphamide as an alkylating agent (nitrogen mustard)
- b. Methotrexate is an anti-metabolite (folic acid analogue), 5-fluorouracil and capecitabine are two drugs used to treat cancer (pyrimidine analogues)
- c. Vinorelbine (vinca alkaloid), paclitaxel (taxane), and doxorubicin are natural products (antibiotics)
- d. Tamoxifen (anti-estrogen), letrozole, and anastrozole are hormones and antagonists (aromatase inhibitors)
- e. Other: trastuzumab (monoclonal antibody), lapatinib (Protein tyrosine kinase inhibitor)

IV. DIAGNOSIS:

Age, stage, tumour grade, tumour type, and lymphovascular status are all standard diagnostic factors. Breast cancer before age 35 is uncommon; patients over 75 have a 17% higher disease-specific mortality than younger patients [13]. The extent of mammography screening has reduced the stage at diagnosis and, as a result, the natural history of breast cancer has changed; prognosis now relies on tumour biology (histological type, grade, lymphovascular invasion, and theranostic marker status). Tumour-infiltrating lymphocytes are associated with a good diagnosis in ER-negative, HER2-negative, and HER2-positive breast cancers [14].

V. TREATMENT:

Treatment recommendations based on breast cancer staging are one of the most consistent prognostic indicators, providing valuable confirmation about cancer detection and treatment status. Breast cancer staging includes tumour size (T 1-4), lymph node association (N 1-3), and the presence of distant metastases (M 0-1).

Lumpectomy alone can be used in stage 0 for Ductal Carcinoma in Situ (0.5cm diameter), but it is combined with adjuvant radiation therapy for larger lesions. Extensive Ductal Carcinoma in Situ (involving two or more quadrants of the breast) necessitates mastectomy; all patients are considered for adjuvant Tamoxifen therapy [15]. For prominent axillary lymphadenopathy, axillary segmentation should be used, and patients with primary cancer (T1 or T2) that does not involve axillary lymph nodes should have sentinel lymph node biopsy.

Systemic Chemotherapy is used in conjunction with radiotherapy to treat early breast cancer. Chemotherapy is used to treat large tumours (>1 cm) and node-positive breast cancer [16]. An assessment of hormone receptor status follows adjuvant endocrine therapy.
Stage IIIa and IIIc cancers are locally advanced and may be resectable or incurable [16]. To treat the resectable type, a modified radical mastectomy, adjuvant Chemotherapy, and radiation therapy are used; neoadjuvant Chemotherapy may be used in some patients to shrink the primary tumour size [17]. An assessment of hormone receptor status follows adjuvant endocrine therapy. A multimodal approach is required to cure stages IIIb, IIIc, and inflammatory breast carcinoma. Initially, neo-adjuvant Chemotherapy is used, and upon the positive response, a significant ‘modified mastectomy tailed by radiation therapy to the chest’/swall and regional lymphatics may be employed [16]. Chemotherapy following breast-conserving surgery may be recommended for some patients [17].

There is no treatment for stage IV breast cancer; treatment focuses on increasing survival rates and improving quality of life. Endocrine therapies are frequently recommended as first-line treatment for ER+ or PR+ cancers with only bone or soft tissue metastases or limited and asymptomatic visceral metastases [16]. Systemic Chemotherapy is best for hormone-refractory, ER- or PR- cancers or symptomatic visceral metastases [18]. Palliation is essential for symptom control, and bisphosphonates can be used for bone metastasis to avoid fractures.

VI. CHALLENGES IN BREAST CANCER TREATMENT:

Many difficulties are encountered when treating breast cancer. These difficulties cause therapy's therapeutic results to decline. Moreover, it lessens the effectiveness of medications and increases their harmful effects. Multidrug resistance (by ABC transporter, P-glycoprotein, MDR associated Protein (MRP1), breast cancer resistance Protein (BCRP), drug resistance in breast cancer, multidrug resistance in breast cancer cells in vitro), alteration of microtubules, altered enzyme, p-53 tumour suppressor gene and cell cycle, alteration in DNA repair processes, cell death response, difficulty treating metastatic stage, inability to reach the target area, and others present challenges during therapy. Many measures, including the following, are taken into consideration to overcome these obstacles: new targeted therapies for the treatment of metastatic breast cancer, drug-induced reversal of tumour resistance, novel antineoplastic agents, a better understanding of breast cancer metastasis at the molecular and cellular level, and the introduction of cutting-edge technologies in metastatic breast cancer detection, including clinicopathologic detection, circulating tumour cells (CTC) detection, and advanced imaging. The conference produced a unanimously positive belief that, in the not-too-distant future, we will be able to prevent and, to a lesser extent, treat metastasis and ultimately spare most people from dying from metastatic disease. Hence, these techniques might be used to get around these difficulties and offer a potential plan for treating breast cancer [19].

MULTIDRUG RESISTANCE (MDR)

Multidrug Resistance (MDR) is a severe issue with chemotherapy-related resistance in treating breast cancer.

Several cancers that were initially susceptible to various anticancer drugs with varying structural and mechanisms of action relapsed and developed resistance to them [20]. The term for this is multidrug resistance (MDR). Although the exact nature of resistance and probable involvement of drug resistance genes in transmitting anticancer medications are still unknown, they may contribute to resistance. Understanding the underlying biological causes of chemotherapy resistance is crucial for developing effective therapeutic options to overcome drug resistance. Many distinct mechanisms may be involved in drug resistance. It might be caused by an increase in ATP-dependent efflux pump activity, leading to lower intracellular drug concentrations. Doxorubicin, daunorubicin, vinblastine, vincristine, and paclitaxel are frequently linked to this resistance. A decline in cell medication uptake might also bring it on. Water-soluble medications may adhere to transporters delivering nutrients and fail to accumulate inside cells.

This mechanism mediates resistance to cisplatin, 8-azaguanine, and 5-fluorouracil [21]. Activating controlled detoxification systems like the cytochrome P450 mixed-function oxidases and increasing DNA repair are two other general mechanisms of resistance.

Lack of drug penetration, altered prodrug activation properties, and altered drug targets are other mechanisms implicated in drug resistance.

ABC TRANSPORTER

ATP-binding cassette transporters) are trans-membrane transporter proteins that have been found in cancer cells that are resistant to anticancer medications. It carries out biological operations using the energy produced by adenosine triphosphate (ATP) breakdown. ABC transporters can comprise three functional groups: Importers facilitate the absorption of nutrients (amino acids, carbohydrates, ions, and other hydrophilic molecules) into the cell. Drugs and poisons are pumped out of the cell by exporters. The last group of ABC proteins is involved in translation and DNA repair. Human ABC genes have been discovered so far, and based on the sequence homology and domain organization of these genes, they have been classified into seven subfamilies (ABCA-ABCG) [22].

The trans-membrane domain (TMD), often referred to as the membrane-spanning domain or the integral membrane domain, and the nucleotide-binding domain is two different domains in all ABC family members (NBD). TMD makes conformational changes to recognize a range of substrates and move them across the membrane. TMDs have a varied structure and sequence that reflects the wide range of chemical substrates that can be transported. The cytoplasmic NBD, also known as the ATP-binding cassette (ABC) domain, has a stable sequence and structure where ATP-binding occurs. P-glycoprotein (PGP), multidrug resistance-related
protein 1 (MRP1), and breast cancer resistance protein (BCRP) are the primary ABC targets for research. Transporters are connected to the rise in breast cancer drug resistance [23].

P-Glycoprotein:
The first ABC transporter identified as being overexpressed in breast cancer cell lines, P-glycoprotein (PGP), showed MDR and had a widespread tissue distribution.

Recently, mouse PGP was described, which shares 87% of the sequence morphology with human PGP in the drug-binding state [24]. PGP is a 12-trans-membrane domain multidrug efflux pump with two ATP-binding sites and a broad spectrum of activity. It aids in removing vinblastine, vincristine, doxorubicin, daunorubicin, etoposide, and paclitaxel from cells, among other neutral and cationic hydrophobic substances. The medication is frequently extracted straight from the cytoplasmic side of the lipid bilayer for transport through PGP.

Lipids are necessary for drug-stimulated ATPase activity, and most PGP substrates are quickly partitioned into the plasma membrane.

MDR-Associated Protein (MRP1)
MRP1 was expressed in a variety of organs and cell types, including breast cancer cell lines [25].

Several studies have shown that cells that overexpress MRP1 develop resistance to several anticancer medications, including doxorubicin [26]. Drug efflux transporter MRP1 has a wide range of substrate specificity. Glutathione stimulates MRP1-mediated transport for several medicines.

The ATP bound at NBD2 is then hydrolyzed, and the subsequent release of ADP from NBD2 partially returns MRP1 to its original conformation, allowing the NBD1 to be released, completing the cycle [27].

Breast Cancer Resistance Protein (BCRP)
Anticancer drugs such as mitoxantrone, camptothecins, anthracyclines, flavopiridol, and anti-folates are linked to BCRP expression in various tumours, leading to drug resistance. In contrast to PGP and MRP1, the BCRP protein only has one transmembrane domain and one nucleotide-binding domain. A disulfide bridge connects two BCRP molecules to form a functional homodimer [28].

Microtubule alteration
Paclitaxel binds to the -subunit of tubulin in microtubules, suppressing microtubule dynamic instability and ultimately causing mitotic arrest and cell death. Overexpression of the -tubulin III isotype has been linked to paclitaxel resistance [29]. Moreover, overexpression of β tubulins types I–IV may be associated with resistance to docetaxel therapy [30].

STRATEGIES USED TO OVERCOME TUMOR RESISTANCE
Pharmacogenomics and imaging techniques
The primary strategy for combating drug resistance is to screen for factors identified as causing or conferring resistance to Chemotherapy. It prevents patients from receiving unnecessary, ineffective, and potentially toxic treatment. With the initiation of DNA microarray analysis with a whole human genome platform, there is a faith that breast cancer patients can be stratified according to their "molecular structure". Based on expression arrays and tissue samples from NuSeverales have been identified as potential therapeutic targets in heavily pre-treated breast cancer patients. New therapeutic targets. The drug development programme began with the assistance of several genes that were found to be highly amplified, including FGFR1, ADAM9, PNMT, and NR1D1, and they may also improve the efficacy of breast cancer therapy [31].

Because of their ability to overcome P-gp drug resistance, novel microtubule destabilizing agents, such as pseudoelastic acid B, are being researched. XRP-9881 (RPR-109881A) is a new taxoid that is being developed to combat the problem of taxane resistance. XRP-9881 is minimally recognized by P-gp and has shown preclinical anti-tumour activity in vitro and in vivo, as well as training in a Phase II trial of patients with MBC who had previously received taxoid chemotherapy [32].

novel anticancer agents
Newer anticancer drugs not subject to these common tumour resistance mechanisms may provide new opportunities in patients who are currently challenging to treat due to resistance.

Agents to combat specific resistance mechanisms, such as BRCA mutations, are being researched. Poly (ADP) polymerase (PARP) inhibitors may target BRCA-related breast cancers specifically. PARP inhibitors have been shown to have limited activity in breast
Advanced Imaging Techniques for Breast Cancer

Multidimensional (e.g., threedimensional and above) and multimodality (i.e., a combination of various modalities) imaging are used in cutting-edge imaging technology.

Scientists compare the detection potential of cancer imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT), and the smaller physical footprint but more prevalent ultrasound. Whole-body imaging is essential in surveying and potentially targeting all possible sites and primary lesions for breast cancer metastases. Only PET currently provides inherent three-dimensional capability, but its clinical limitation to a single tracer (e.g., fluorodeoxyglucose) limits its effectiveness in pinpointing disease type and staging more specifically. Advanced imaging has grown to be a crucial part of MBC management. Breast cancer metastases will likely be better diagnosed and targeted. Possible therapies will be more objectively estimated thanks to integrating sophisticated tools and cutting-edge computer imaging techniques [33]. This should all enhance patient outcomes.

Chemotherapeutic agents

The following are some of the common breast cancer treatment regimens. Cyclophosphamide inhibits DNA replication and cell division and is used to treat breast cancer metastasis. Hepatic intracellular enzymes convert this prodrug into active metabolites (i.e. four hydroxy Cyclophosphamide, aldophosphamide, acrolein, and phosphor amide mustard) [33]. The drug has been used as adjuvant therapy in combination with CMF or an anthracycline for treating breast cancer [34]. Platinum compounds such as carboplatin and cisplatin treat breast cancer as monotherapy or a combination regimen [35]. Platinum compounds have been studied for their effect on DNA conformation and stability, and several platinum DNA adducts have been identified in vivo and in vitro. Early studies quantified the impact of these dissimilar lesions on DNA replication, their ability to introduce mutations, and their susceptibility to DNA repair procedures. Platinum (IV) compounds may cause additional DNA damage, possibly by degrading to platinum (II) compounds in the cell [36]. Carboplatin therapy was effective in 20-35% of patients with metastatic breast cancer who received monotherapy [37, 38].

The most commonly used taxanes that cause mitotic arrest by stabilizing cellular microtubule elements are paclitaxel and docetaxel. These agents have been used as single or combined [39]. In breast cancer, a weekly management schedule of these agents has been reported to be well tolerated with little toxicity [40,41]. Despite the risks, multidrug combination regimens are effective in treating breast cancer.

Capecitabine is an oral fluoropyrimidine prodrug that, upon infusion, transforms into 5-FU via the thymidine phosphorylase enzyme, producing similar effects as 5-FU. It has been used with taxanes to treat metastatic breast cancer [42].

Gemcitabine (or difluoro deoxy cytidine) is a pyrimidine nucleotide that inhibits RNA synthesis and DNA replication and is used to treat a variety of cancers, including lung, bladder, and breast cancer. Weekly IV injections of gemcitabine are well tolerated.

Vinorelbine binds to tubulin, causing mitosis metaphase to be disrupted. According to various studies [43-45], this drug has shown promising results in advanced breast cancer.

CONCLUSION

During Chemotherapy, cancer patients face several challenges and opportunities. Due to the complexity of the mechanisms involved, determining the precise role of ABC transporters in breast cancer MDR has been difficult.

Investigations into the expression of these proteins in breast cancer cells and tumour samples have frequently revealed inconclusive results. Differences in the experiment of all techniques have made direct comparisons of results between studies complex. Although several clinical studies have found that high levels of tumour ABC transporters are linked to tumour progression, no clear link has been found between expression levels and tumour sensitivity to Chemotherapy or patient outcome. A better understanding of this complex and dynamic system is required to develop therapeutic strategies that avoid MDR and effective methods of inhibiting MDR components from improving the efficacy of our currently widely used chemotherapies. Several approaches are being developed to address these challenges, including pharmacogenomics and imaging techniques, drug-induced tumour resistance reversal, novel antineoplastic agents, and new targeted therapies for treating MBC.

This review discusses advanced imaging techniques used in breast cancer that aid in cancer diagnosis and treatment. This review also serves as a foundation for developing novel therapies with improved therapeutic efficacy and no limitations.
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