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Chapter- 14

Therapeutic and Diagnostic Approaches to Combat Breast Cancer

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Abstract:

Breast cancer is one of the life-threatening diseases in women worldwide, leading to the mortality of millions of people all around the world. The objective of this review is to discuss various strategies for breast cancer treatment. The increased prevalence of breast cancer globally in recent years has increased challenges to clinicians. The availability of appropriate detection tools for early detection is the major part of the clinical management of breast cancer patients in the present situation. Together with the current imaging techniques, molecular biomarkers based research has gained huge attention in disease management. Chemotherapeutic drugs significantly reduce the mortality rate of breast cancer. Over past fewyears, substantial advances has been made in the discovery of cytotoxic, hormonal and targeted drugs for treating breast cancer. The therapeutic response is dependent on a variety of factors, including stages, subtypes, metastasis, etc. Toxicity and chemotherapy resistance are major limitations in the treatment of patients with Breast Cancer. Further study is needed in order to maximise benefit, whilst minimising toxicity.

Introduction:

Breast cancer (BC) is the most widespread type of cancer amongst women worldwide. Approximately 80% of patients with BC are over 50 years old, and the risk increases with age. The risk factors include a history of BC, obesity, height, smoking, drinking alcohol, early or late menstruation, a sedentary lifestyle, and hormone replacement therapy (Bodewes et al., 2022; Rami et al., 2023; Yadav et al., 2024). Breast cancer can be classified into different types according to the sites and invasiveness and by the presence or absence of a hormonal receptor (HR+/-), progesterone receptors (Onitilo et al., 2009). Histologically, the breast tumours are divided into preinvasive and invasive subtypes involving ductal and lobular compartments. Ductal and lobular subtypes are again classified into DCIS (Ductal carcinoma in situ), IDC (Invasive ductal carcinoma), LCIS (lobular carcinoma in situ) and ILC (Invasive lobular carcinoma) (Table 1).

The estrogen receptor (ER) is a major driver of the majority of breast cancers as it is expressed in 75% of breast cancers overall. It is more frequently related with postmenopausal women and there is a 99% survival rate at ten years. The most common receptors that are overexpressed in

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breast cancer cells are part of the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases: EGFR and HER2 (human epidermal growth factor receptor 2) are overexpressed in approximately 40% and 25% of breast cancers respectively and are believed to be responsible for more aggressive tumor behaviour and poor prognosis (Nuciforo et al., 2015). Triple negative breast cancer (TNBC) is defined by the lack of expression of both estrogen and progesterone as well as the HER2 protein and is often associated with an unfavorable prognosis as no treatment is yet available for this particular breast cancer subtype (Gluz et al., 2009). Metastatic breast cancer (MBC) is a serious health problem worldwide, presenting mostly together with bone metastases as the most common site of disease recurrence. Metastases secondary to BC negatively impact patient survival and quality of life. Current strategies to decrease a woman's risk of developing breast cancer include primary prevention, such as avoiding tobacco, exogenous hormone use, and excess exposure to ionizing radiation, maintaining a normal weight, exercising, breastfeeding, eating a healthy diet, and minimizing alcohol intake. Though the mortality rates of breast cancer have changed a little over the years, the survival rate, however, has also increased due to awareness campaigns, early detection programs, and continuous research to develop new drug molecules or new formulations for the treatment of the disease (Roy et al., 2022).

Treatment options for early-stage breast cancer, including chemotherapy, radiation therapy, surgery, hormone therapy, and targeted therapy, have demonstrated efficacy, but for patients with the metastatic form of the disease, response rates are low (Rivera et al., 2010; Madhu et al., 2022, 2023). In the subsequent section, we provide a comprehensive overview of various therapeutic agents. These drugs could be classified in different ways based on their chemical nature, molecular target, mode of action, or effectiveness (Table 2).

Our main focus will be to summarize recent trends in breast cancer diagnosis and treatment as reported in recent research papers and discuss future perspectives for effective breast cancer therapy.

Table 1: Types of breast cancers based on histology.

Type	%	Occurrence	Reference
Ductal carcinoma in situ (DCIS)	10-15%	Ductal carcinoma in situ (DCIS) is a non-invasive cancer where abnormal cells have been found in the lining of the breast milk duct. The atypical cells have not spread outside of the ducts into the surrounding breast tissue.	Elizabeth et al, 2015
Lobular carcinoma in situ (LCIS)	1-2%	LCIS is recognized by its conformity to the outline ofthe normal lobule, with expanded and filled acini.	Cutuli et al, 2015
Invasive Ductal Carcinoma (IDC)	70%	Invasive Ductal Carcinoma (IDC) is an invasive cancer where abnormal cancer cells that began forming in the milk ducts have spread beyond the ducts into other parts of the breast tissue. Invasive cancer cells can also spread to other parts of the body. It is also sometimes called infiltrative ductal carcinoma.	Li et al, 2005

Invasive lobular Carcinoma (ILC)	5-10%	ILC starts in lobules (where breast milk is made) andthen spreads into the nearby breast tissue. Like IDC, it may metastasize and spread to other parts of the body	Reed et al, 2021

Table 2: Table listing therapeutic agents against breast cancer.

Type of drug	Examples	Reference
Cytotoxic drug	i. Alkylating agent Ex, Cyclophosphamide ii.Platinum complex Ex-Cisplatin and Carboplatin iii. Antimetabolites Ex, Methotrexate, Gemcitabine iv. Microtubule damaging agent v. Antibiotics Ex, Doxorubicin Hydrocloride	Chaurasia et al, 2023
Targeted drug	i. Tyrosine protein kinase inhibitor Ex, Lapatinib ii. Unarmed Monoclonal antibody Ex, Transtuzumab iii. mTOR inhibitor Ex-Everolimus iv. CDK4/6 inhibitor v. EGF receptor inhibitor Ex-Afatinib vi. Anti-HER2 antibodies vi. Angiogenesis inhibitor	Jacobs et al, 2022
Hormonal drug	i. Estrogen Ex,Tamoxifen ii. Aromatage inhibitor Ex, Letrozole iii. GnRH iv. Anti-androgen	Abraham & Abraham, 2016

Diagnosis:

Imaging tests

Mammography

Mammography (MG) is preferred strategy for screening and diagnosing BC and helps doctors obtain clinic information on BC patients. The evidence suggests that the mortality rate of BC patients could be reduced 30% - 40% though early MG screening (Ayer, 2016).

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.

Magnetic resonance imaging (MRI)

MRI is a powerful imaging tool that produces high-resolution images without requiring the application of harmful radiation. A special dye called a contrast medium is given before the scan to help create a clear picture of the possible cancer. This dye is injected into the patient's vein. National Comprehensive Cancer Network considers breast MRI as a useful adjunct to diagnostic mammography, if needed, in some specific situations due to poor selectivity and its dependence contrast media (Kerlikowske et al., 2011).

Biopsy

Breast biopsy

The only definitive method for diagnosing breast cancer is with a breast biopsy. There are several different types of breast biopsies (Palmer and Tsangaris, 1993).

Two types of needle biopsies are used to diagnose breast cancer: fine needle aspiration cytology (FNAC) and core needle biopsy (CNB). CNB uses a wider needle to remove a larger sample of tissue. This is usually the preferred biopsy technique.

Sentinel lymph node biopsy

When cancer spreads through the lymphatic system, the lymph node or group of lymph nodes the cancer reaches first is called the "sentinel" lymph node. In breast cancer, these are usually the lymph nodes under the arms called the axillary lymph nodes.

Analyzing the biopsy sample

Tumor features

Examination of the tumor under the microscope is used to determine if it is invasive or non-invasive (in situ), ductal, lobular, or another type of breast cancer and whether the cancer has spread to the lymph nodes.

Estrogen receptors (ER) and progesterone receptors (PR)

Testing for ER and PR helps determine both the patient's risk of recurrence (risk of the cancer coming back) and the type of treatment that is most likely to lower the risk of recurrence. Generally, hormonal therapy, also called endocrine therapy or hormone-blocking therapy, reduces the chance of recurrence of ER-positive and/or PR-positive cancers.

Human epidermal growth factor receptor 2 (HER2)

The HER2 status of the cancer helps determine whether drugs that target the HER2 receptor. This test is only done on invasive cancers.

Genomic tests to predict recurrence risk

Breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) are commonly used gene markers for breast cancer susceptibility (Michael et al., 2017). They are tumor suppressor genes involved in repair of DNA double-strand breaks that are responsible for breast cancer. Nowadays, with the reduction in the cost of DNA sequencing, individual genome sequencing may be affordable by middle-class populations, and this could be a new method in preventing breast cancer. If a woman have a family history of breast cancer, it is wise to do a screen especially on hereditary cancer susceptibility genes such as BRCA1 or BRCA2. The risk of breast cancer could then be evaluated based on the screening results and prevention advice could be offered personally.

Proteomic Biomarkers

Numerous protein biomarkers such as RS/DJ-1, p53, heat shock protein 60 (HSP60), HSP90, mucin 1 (MUC1) and human epidermal growth factor receptor 2 (HER2) antigens have been investigated for clinical applications. Le et al., 2001 found that women with newly diagnosed breast cancer have significantly higher serum RS/DJ-1 levels than healthy subjects.

Additional test

Ki-67 index: Ki-67 is a protein in cells that increases as they prepare to divide. If there is a high percentage of cells with the Ki-67 protein in the tumor, it means that the cells are dividing rapidly. The Ki-67 index, which is also called a proliferative index, is an indicator of how quickly the tumor cells are multiplying. When the genomic tests cannot be used for people with stage I or II breast cancer who have been through menopause, the Ki-67 index may be used to help patients and their doctors make decisions about whether chemotherapy and hormonal therapy should be given following surgery (Inwald et al., 2013).

Immunohistochemistry 4 (IHC): This test uses ER, PR, and HER2 status as well as the Ki- 67 index from a sample of tumor to estimate the risk of the cancer coming back within 10 years after diagnosis (Kroese et al., 2007). It can be used for people whose cancer has not spread to the lymph nodes or has only spread to 1 to 3 lymph nodes. This test can help patients and their doctors make decisions about whether chemotherapy should be given before hormonal therapy.

Breast Cancer Index (BCI): This test uses information from 11 genes to estimate the risk of the cancer coming back within 5 to 10 years after a diagnosis. It is used for people whose cancer has not spread to the lymph nodes or has only spread to 1 to 3 lymph nodes. For a patient who has had 5 years of hormonal therapy and who has no evidence of cancer recurrence, this test can help patients and their doctors make decisions about whether additional hormonal therapy with tamoxifen (Bartlett et al., 2022).

Common treatments for all types of breast cancer

An Overview of diagnostic and therapeutic approaches to treat breast cancer is shown in figure (Figure 1 and table 3).

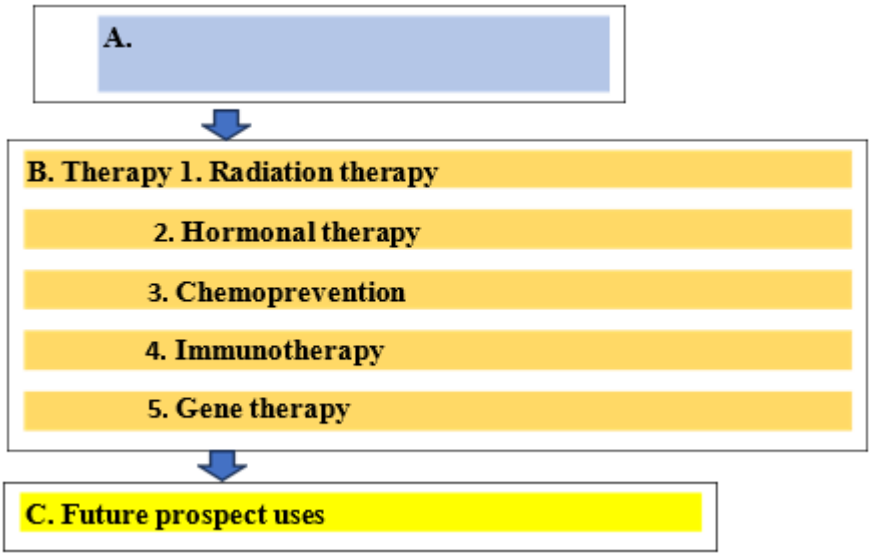

Figure 1. Schematic diagram representing approaches against breast cancer management

Surgery

The most standard breast surgery approaches are either total excision of the breast (mastectomy), usually followed by breast reconstruction, or breast-conserving surgery (lumpectomy).

Radiation Therapy

Radiotherapy is local treatment of BC, typically provided after surgery and/or chemotherapy. It is performed to ensure that all of the cancerous cells remain destroyed, minimizing the possibility of breast cancer recurrence. This therapy is favorable in the case of metastatic or unresectable breast cancer (Yang et al., 2013).

Endocrine therapy

Endocrine therapy is a major treatment option for the majority of MBC expressing hormone positive receptors (estrogen and/or progesterone) in pre- and post-menopausal women (Salkeni and Hall, 2017). The estrogen receptor (ER) has a vital role in mediating transcription for a wide range of genes responsible for proliferation, invasion and angiogenesis in BC (Brisken and Malley, 2010). ER+ tumors tend to metastasize to the bone (Pareek et al., 2019). Endocrinal therapy might be used either as a neoadjuvant or adjuvant therapy in patients with Luminal-molecular subtype of BC; it is effective in cases of breast cancer recurrence or metastasis. Tamoxifen (ER antagonist) 20 mg/day for 5-10 years is a standard in case of premenopausal patients (Puhalla et al., 2009). At diagnosis, 75% of breast tumors are ER+ and can potentially respond to tamoxifen, aromatase inhibitors, or other hormonal therapies. (Lumach et al., 2011; Tremont, 2017). Aromatase inhibitor (AIs) (both nonsteroidal and steroidal) and tamoxifen are valid options in case of postmenopausal patients (Davies et al., 2013).

Chemotherpy (CT)

In high-risk patients, systemic chemotherapy is generally recommended. Currently, several chemotherapeutic agents are used as monotherapy or in combination with others for MBC (Abotaleb et al., 2018; Hernandez-Aya & Ma, 2016). The most commonly used single-agent cytotoxic drug classes include taxanes (docetaxel, paclitaxel, nab-paclitaxel), anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin), and capecitabine (Abotaleb et al., 2018; Hernandez-Aya & Ma, 2016). The benefit from CT is more pronounced in ER-negative tumors. CT is recommended in the vast majority of TNBC, HER2-positive breast cancers, and in high-risk luminal tumors. In ER-positive tumors, CT at least partially exerts its effect by induction of ovarian failure (Shao et al., 2012).

Neoadjuvant Chemotherapy (NAC)

Neoadjuvant chemotherapy was initially administered for non-metastatic but inoperable BC, defined as unreachable tumors (Chira et al, 2013). Studies demonstrated that chemotherapy administered before surgery is as effective as administered after surgery (Broët et al., 1999; van der Hage et al., 2001; Fisher et al., 1998)

Adjuvant Chemotherapy

Adjuvant chemotherapy is administered to BC patients with lymph nodes metastases or a high risk of recurrence (Peto et al., 2012).

Targeted therapies

Targeted therapy is the current standard of care to treat HR+ and HER2+ BC, but it cannot be administered to patients with Triple negative breast cancer (TNBC) as these tumors lack the expression of these biomarkers. Hence, the next logical step is to identify biomarkers associated with TNBC to develop specific targeted therapies. Several emerging targeted therapies are being clinically trailed with limited or mixed results.

HER2-Directed Therapies

HER2+ breast cancer (HER2+ BC) is characterized by drug resistance and a high rate of metastasis. Targeted therapy drugs have been shown to greatly improve the prognosis of HER2+ BC patients, but drug resistance or severe side effects have limited the clinical application of targeted therapy drugs. Various strategies are being researched to overcome drug resistance and to attain a more effective treatment. The main function of this HER2 oncogene is to encode transmembrane receptor tyrosine kinase (Witton et al., 2003). Tyrosine kinase inhibitors competitively inhibit tyrosine phosphorylation and block tyrosine kinase enzyme activity, thus, resulting in downregulation of many cellular functions (Scaltriti et al., 2009). Neratinib (NERLYNX, Puma Biotechnology, Inc., CA, USA), an irreversible tyrosine kinase inhibitor (TKI) of HER1/HER2/HER4, has been reported to significantly improve the 2-year invasive disease-free survival after trastuzumab-based adjuvant therapy in HER2+ BC (Chan et al., 2016).

Immunotherapy

Supplementing our immune system by devising immunotherapy strategies is another highly-specific and largely promising approach to address the problem of late-stage cancer therapeutics (Karlitepe et al., 2015). An immunologic therapeutic strategy is mainly used for tumors overexpressing HER2; they represent about 20% of MBC. This cancer has a poor prognosis, and treatment is difficult (Mercogliano et al., 2023).

Recently, immunotherapy becomes a hot spot in cancer therapy, and it shows great potential in clinical use. Programmed cell death 1 (PD1) is a membrane protein expressed in various immune cells, including T cells, which can be engaged by its specific ligand to block the immune system. Programmed cell death receptor ligand 1 (PDL1), a ligand of PD1, is detected in 20% of TNBC and in 50% of all breast cancers (Guan et al., 2016; Sabatier et al., 2015). Atezolizumab, an anti-PDL-1 antibody, has demonstrated safety and efficacy in a phase I study for metastatic TNBC patients (Emens et al., 2019). The safety and efficacy of avelumab, another anti-PDL-1 antibody, was evaluated in the phase Ib JAVELIN study in patients with locally advanced or metastatic BC, including TNBC (Dirix et al., 2018).

Table 3: Table shows anticancer drugs from various categories for treatment of breast cancer.

Drug	Class	Indication
Endocrine therapy		
Fulvestrant	Pure ER antagonist competitively inhibits the binding of natural estradiol.	Treatment of postmenopausal women with ER-positive locally advanced or MBC for disease relapse on or after adjuvant anti-estrogen therapy or disease progression following anti-estrogen therapy.
Exemestane	Aromatase inactivator prevents conversion of androgens to estrogens.	Treatment of advanced breast cancer in postmenopausal women.
Cytotoxic agent		
Capecitabine	Antimetabolite, prodrug for 5-fluorouracil.	Monotherapy: treatment of patients with locally advanced or MBC after failure of taxanes and an anthracycline-containing chemotherapy regimen.
Ixabepilone	Microtubule-stabilizing agent	Monotherapy: treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, ataxane.

Targeted therapy		
Trastuzumab	Monoclonal antibody that blocks signaling through HER2.	Monotherapy: treatment of HER2-overexpressing breast cancer in patients who have received at least two chemotherapy regimens.
Lapatinib	Small molecule inhibitor of EGFR and HER2.	In combination with capecitabine for the treatment of patients with advanced or MBC whose tumors overexpress HER2.

Therapeutic response based on gene expression

Breast cancer diagnosis by breast examination, mammography, breast ultrasound, MRI, and other imaging modalities can help identify tumors. Based on mRNA gene expression levels, BC can be divided into molecular subtypes (Luminal A, Luminal B, HER2-enriched, and basal- like). By evaluating the presence of biomarkers such as hormone receptors (HRs), excess levels of human epidermal growth factor receptor 2 (HER2) protein, and/or extra copies of the HER2 gene (Hammond et al., 2010; Wolff et al., 2014), treatments that are most effective against a particular type of breast cancer can be evaluated and administered (Table 4).

Table 4: Sub-types of breast cancer with distinct prognostic features and response to therapies.

BC Subtypes	Molecular subtype	% B.C	Histological grade	5 yr survival rate	Prognosis	Response to therapy	Reference
Triple negative	ER-, PR-, HER2-	15-20	Grade III	76.9%	Poor	Chemotherapy	Neve et al, 2006; Charafe et al, 2006
HER+2	ER-, PR-, HER2+	10-15	Grade III	84%	Worse	Chemotherapy+ Targeted therapy	
LuminalB	ER+, PR+, HER2+/-	40	Grade II	94.3%	Intermediate	Endocrine+ Chemotherapy	
LuminalA	ER+, PR+, HER2-	20	Grade I	90.5%	Good	Endocrine	

Currently used drugs in clinical trials for treatment of breast cancer

Drugs used to treat breast cancer are considered systemic therapies because they can reach cancer cells almost anywhere in the body. Some can be administered orally, through intramuscular route, or as an intravenous injection or infusion. Depending on the type of breast cancer, different types of drug treatment might be used. In this article we have compiled information about mechanism of action, approval status, available novel and targeted drug

delivery systems which are under clinical trial (Table 5) (Voli et al., 2020; Caulfield et al., 2019). Moreover, the novel formulations are getting humungous attentions of researchers as these can provide targeted treatment which is devoid of side effects and improve quality of life (Maji et al., 2014; Wong et al., 2006).

Table 5: List of various drugs in clinical trial for various conditions of breast cancer.

Cellular target	Agent	Application	Clinical study
EGFR	Cetuximab and paclitaxel	Advanced BC	Phase I
VEGF	Bevacizumab	Metastatic BC	Phase I/II
	Bevacizumab/trastuzumab, carboplatin/nab-paclitaxel versus trastuzumab carboplatin/nab-paclitaxel	HER-2 positive metastatic BC	Phase II
TRAIL receptors	TRAIL	BC, gynaecologic malignancies	Phase I
Ras, farnesyl transferase	Tipifarnib and gemcitabine	Metastatic BC	Phase II
COX-2	Celecoxib	BC adjuvant	Phase III
EGFR/HER2	Lapatinib and capecitabine versus capecitabine	Advanced BC	Phase III

Use of nanomedicine in current and future research for breast cancer management

There are several types of nanomaterials being used widely, such as solid-lipid nanoparticles, liposomes, and polymers (Montesinos et al., 2021). As of today, only few nanomedicine products have gained US Food and Drug Administration (FDA) approval, and Doxil and Abraxane are the two most successful nano-formulations already widely used for breast cancer treatment in clinical trials (Barenholz et al., 2012; Minckwitz et al., 2013). It is expected that strong collaboration with experts in pharmacokinetics, toxicology, immunology and oncology will become essential. Many *in vitro, in vivo* xenograft and clinical studies are required for development of nanodrugs in future.

Conclusion

Drug discovery for Breast Cancer has always been an area of interest for researchers as even today there is no drug/drug combination which can promise 100% side effects/adverse effects free treatment of Breast Cancer. In this review, we aimed to summarize the current knowledge of breast cancer with an emphasis on classification, available treatment strategies. The value of local and systemic therapies in breast cancer has been well established. For early breast cancer, surgery-based local and systemic treatments are the standard of care. For metastatic breast cancer, chemotherapy-based systemic treatments remain the preferred option but surgery is only used for palliative therapy in selected patients. However, survival benefits of traditional treatment

strategies were limited. The emergence of targeted therapy and immunotherapy further changed the treatment pattern of early and metastatic breast cancer.

Multiple companies now offer whole genome sequencing of a patient's tumor to identify targetable mutations for treatment, and increasingly treatment trials are being designed based on a given genetic alteration rather than on the site of tumor origin. Tamoxifen is also FDA approved for the prevention of breast cancer in premenopausal high-risk women. Atezolizumab is approved in triple-negative breast cancer, while denosumab is approved in case of metastasis to the bones (Heimes et al., 2018; Steger et al., 2011). Another important issue in BC treatment is the acquisition of treatment resistance. This is a common phenomenon for either endocrine therapy, anti-HER2 therapy and chemotherapy. Further studies must provide much-needed data on predicting response to therapies, revealing modes of resistance to therapies, and maximizing the patient's benefit.

Conflict of interest:

None

Reference:

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