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A Brief Review on Breast cancer treatment and current challenges

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Abstract

Cancer is a global disease, so rational and effective treatment is needed. Breast cancer is one of the most common cancers in a woman and now the number of patients is increasing day by day. Therefore, development and research are underway for the effective treatment of breast cancer. Breast cancer treatment depends on the stage of cancer and the risk, based on this medical agents should be employed on patients to prevent breast cancer. In addition, breast cancer survival rates are rising which is good news for science but on the other hand the side effects of treatment present new challenges. An early-stage cancer diagnosis can save a patient's active or healthy life due to long-term and varied treatments that can be used for cancer otherwise breast cancer is a life-threatening disease. Breast cancer survivors not only have negative side effects of cancer treatment but also, have many other issues of previous treatment so it is a challenge for researchers. As a result, this review article deals with the effective treatment of breast cancer and its side effects. This review will help researchers better understand the long-term medical implications for breast cancer.

Key words:
Cancer,
Breast cancer,
Treatment.

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Introduction

Cancer is a leading cause of death worldwide viz. characterized by uncontrolled growth of abnormal cells in body. Worldwide deaths, going to rise from 7.6 million deaths in 2008 to 13.2 million by 2030 as per world health organization (WHO) [1]. As the normal body cells grow, divide into new cells, and die in well-ordered manner but instead of dying, cancer cells continue to grow and multiply in an uncontrolled manner to form tumors. Cancer cells often travel to other parts of the body, where they begin to grow in uncontrolled manner and form new tumors that replace normal tissue viz. referred to as metastasis. No matter where a cancer may spread, it is always named for the place where it started. For example, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Extremely slow progress in cancer diagnosis and treatment options owing to dose related side effects, lack of tumor specificity and effective intracellular delivery, poorly predictive preclinical models, development of drug resistance etc. leads to poor prognosis in patients with common metastatic tumors such as breast, prostate, lung and gastrointestinal cancers [2]. Breast cancer is a malignant tumor that starts in the tissues of the breast that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Most breast cancers begin in the cells that line the ducts called as ductal carcinoma. Some begin in the cells that line the lobules called as lobular carcinoma while a small number start in other tissues [3,4]. To understand breast cancer it's crucial to have some basic knowledge about the anatomy of the breasts which is shown in **Figure 1.1.** The breast is made up primarily of lobules (milk-producing glands), ducts (tiny tubes that carry the milk from the lobules to the nipple), and stroma (fatty tissue and connective tissue surrounding the ducts and lobules, blood vessels, and lymphatic vessels).

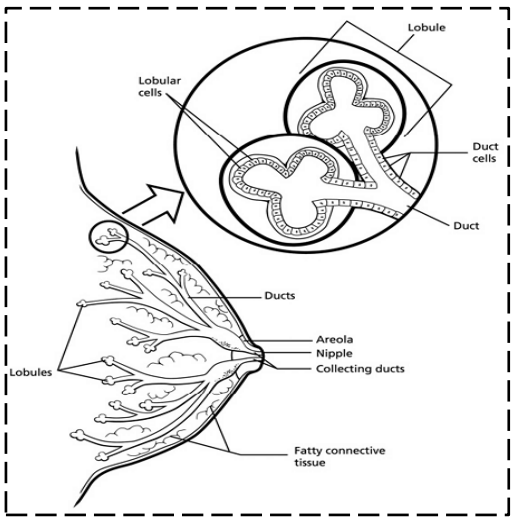

Figure 1. 1 Normal Structure of the Breast

Breast Cancer Pathophysiology

Although normal cells are protected by several protein clusters and pathway, they commit suicide (apoptosis) when they are

they are no longer needed. PI3K/AKT and RAS/MEK/ERK are the protective pathways and sometimes the genes along these protective pathways are mutated in a way that turns them permanently "on", rendering the cells incapable of committing suicide when they are no longer needed. This is one of the causes of cancer in combination with other mutations. Normally, the PTEN protein turns off the PI3K/AKT pathway when the cell is ready for suicide and mutation in gene of PTEN protein leads to PI3K/AKT pathway stuck in the "on" position, and the cancer cell does not commit suicide. Overview of signal transduction pathways involved in apoptosis shown in Figure 1.2 and mutations leading to loss of apoptosis can lead to tumorigenesis [5].

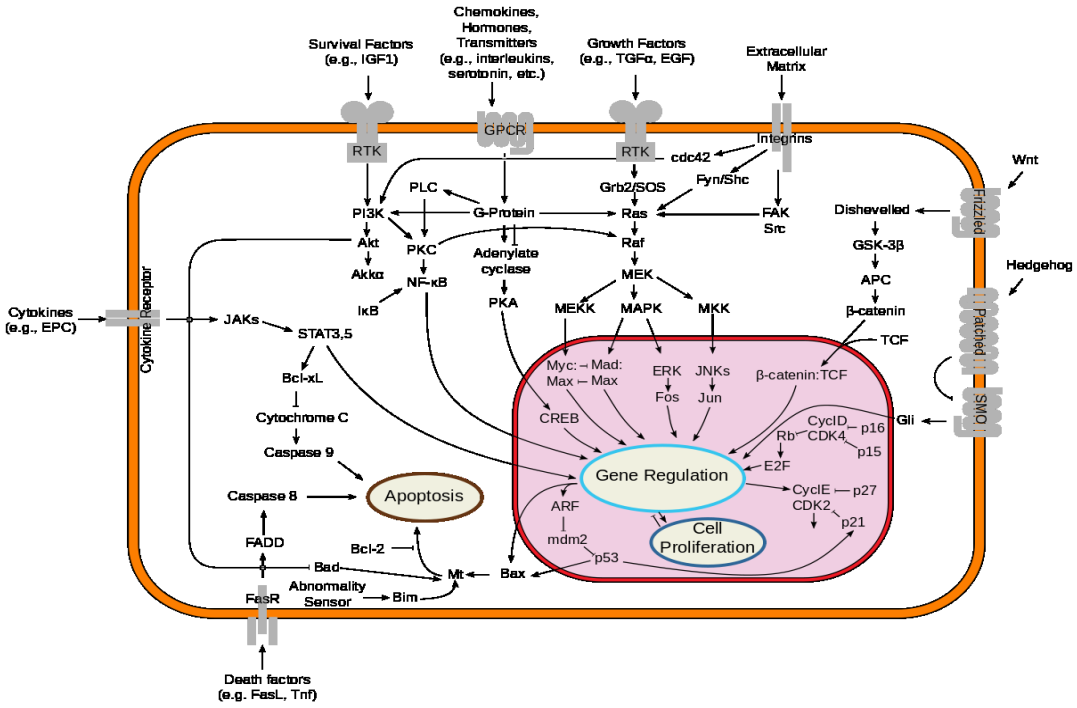

Figure 1.2 Overview of signal transduction pathways involved in apoptosis

Types of breast cancers

There are several types of breast cancer as mentioned in Figure 1.3, but some of them are quite rare. In some cases a single breast tumor can be a combination of these types or be a mixture of invasive and in situ cancer [4].

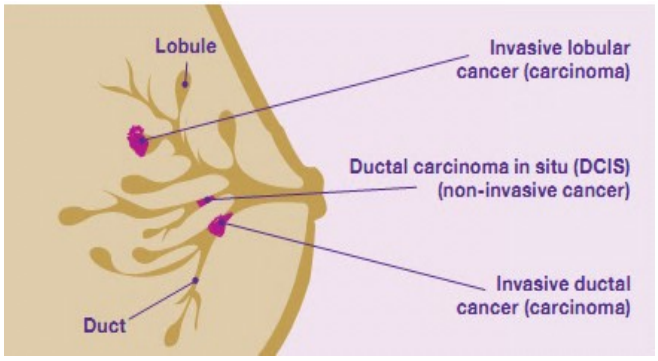

Figure 1.3 Types of Breast Cancer

Ductal carcinoma in situ (DCIS) or Intraductal carcinoma

Most common type of non-invasive breast cancer.

Lobular carcinoma in situ (LICS)

Least common type of non-invasive breast cancer.

Invasive (or infiltrating) ductal carcinoma (IDC)

Most common type of breast cancer. Invasive (or infiltrating) ductal carcinoma starts in a milk duct of the breast, breaks through the wall of the duct, and grows into the fatty tissue of the breast. At this point, it may be able to spread (metastasize) to other parts of the body through the lymphatic system and bloodstream. About 8 of 10 invasive breast cancers are infiltrating ductal carcinomas.

Invasive (or infiltrating) lobular carcinoma

Invasive lobular carcinoma (ILC) starts in the milk-producing glands (lobules). Like IDC, it can spread (metastasize) to other parts of the body. About 1 invasive breast cancer in 10 is an ILC. *Invasive lobular carcinoma may be harder to detect by a mammogram than invasive ductal carcinoma.*

Less common types of breast cancer

Inflammatory breast cancer is uncommon type of invasive breast cancer accounts for about 1-3% of all breast cancers. Triple-negative breast cancer term is used to describe breast cancers (usually invasive ductal carcinomas) whose cells lack estrogen receptors, progesterone receptors, and do not have an excess of the HER2 protein on their surfaces. Paget disease of the nipple is type of breast cancer starts in the breast ducts and spreads to the skin of the nipple and then to the areola (the dark circle around the nipple). It is rare, accounting for only about 1% of all cases of breast cancer. Phyllodes tumor is very rare breast tumor develops in the stroma (connective tissue) of the breast, in contrast to carcinomas, which develop in the ducts or lobules. Angiosarcoma is form of cancer starts in cells that line blood vessels or lymph vessels. It rarely occurs in the breasts.

Special types of invasive breast carcinoma (sub-types of invasive carcinoma)

These are often named after features seen when they are

viewed under the microscope, like the ways the cells are arranged. Some of these may have a better prognosis than standard infiltrating ductal carcinoma. These include adenoid cystic (or adenocystic) carcinoma, low-grade adenosquamous carcinoma (this is a type of metaplastic carcinoma), medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma. Some sub-types have the same or maybe worse prognosis than standard infiltrating ductal carcinoma. These include metaplastic carcinoma (most types, including spindle cell and squamous), micropapillary carcinoma and mixed carcinoma (has features of both invasive ductal and lobular) [4].

Breast cancer chemoprevention

Chemoprevention is the use of drugs to reduce the risk of cancer. Several drugs have been studied for lowering breast cancer risk including tamoxifen and raloxifene that blocks the effect of estrogen on breast tissue. Aromatase inhibitors such as anastrozole and exemestane blocking the production of small amounts of estrogen that post-menopausal women normally make. Other drugs include aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen seem to have a lower risk of breast cancer. Studies have also looked to see if drugs called bisphosphonates may lower the risk of breast cancer. Bisphosphonates are mainly used to treat osteoporosis, but they are also used to treat breast cancer that has spread to the bone [6, 7].

Treatment for Breast Cancer

Main types of treatment for breast cancer include surgery, radiation, chemotherapy, hormonal, targeted and bone-directed therapies (bisphosphonates and denosumab) [8, 9]. Treatments can be classified into broad groups, based on how they work and when they are used such as local versus systemic therapy and adjuvant versus neoadjuvant therapy.

Surgery for breast cancer

Most women with breast cancer have some type of surgery. Surgery is often needed to remove a breast tumor. Options for this include breast-conserving surgery (lumpectomy and quadrantectomy) and mastectomy. Breast reconstruction can be done at the same time as surgery or later on [10].

Radiotherapy

Radiotherapy uses high energy x-rays to destroy any cancer cells left behind in the breast area after surgery and is given to reduce the risk of the cancer returning in the breast. Radiotherapy also affects healthy cells, but they are generally able to recover and repair themselves. Damage to healthy cells can be kept to a minimum by giving small doses of radiotherapy regularly [11].

Chemotherapy

Chemotherapy is treatment with cancer-killing drugs given by oral and intravenous route. The drugs travel through the bloodstream to reach cancer cells in most parts of the body. Chemotherapy is given in cycles, with each period of treatment followed by a recovery period. Treatment usually lasts for several months. It is most effective when combinations of more than one drug are used. Many combinations are being used, and it's not clear that any single combination is clearly the best [12,13]. Clinical studies continue to compare today's most effective treatments against something that may be better.

Some of the most commonly used drug combinations are:

- **CMF:** Cyclophosphamide (Cytoxan®), Methotrexate, and 5- Fluorouracil (fluorouracil, 5-FU)
- **CAF (FAC):** Cyclophosphamide, Doxorubicin (Adriamycin®), and 5-Fluorouracil
- **AC:** Doxorubicin (Adriamycin®) and Cyclophosphamide
- **EC:**Epirubicin (Ellence®) and Cyclophosphamide
- **TAC:** Docetaxel (Taxotere®), Doxorubicin (Adriamycin®) and Cyclophosphamide
- **AC → T:** Doxorubicin (Adriamycin®) And Cyclophosphamide followed by Paclitaxel (Taxol®) or Docetaxel (Taxotere®). Trastuzumab (Herceptin®) may be given with the Paclitaxel or Docetaxel for HER2/neu positive tumors.
- **A → CMF:** Doxorubicin (Adriamycin®), followed by CMF
- **CEF (FEC):** Cyclophosphamide, Epirubicin and 5-Fluorouracil (this may be followed by docetaxel)
- **TC:** Docetaxel (Taxotere®) and Cyclophosphamide
- **TCH:** Docetaxel, Carboplatin and Trastuzumab (Herceptin®) for HER2/neu positive tumors Other chemotherapeutic drugs used to treat breast cancer include cisplatin, Vinorelbine (Navelbine®), Capecitabine (Xeloda®), Liposomal Doxorubicin (Doxil®), Gemcitabine (Gemzar®), Mitoxantrone, Ixabepilone (Ixempra®), Albumin-Bound Paclitaxel (Abraxane®) and Eribulin (Halaven®). The targeted therapy drugs Trastuzumab and Lapatinib (Tykerb®) may be used with these chemotherapeutic drugs for tumors that are HER2/neu-positive.

Hormonal Therapy

Hormone therapy is another form of systemic therapy. It is most often used as an adjuvant therapy to help reduce the risk of the cancer coming back after surgery, but it can be used as neoadjuvant treatment, as well [14]. Hormonal agents are Tamoxifen, Toremifene (Fareston®), Letrozole (Femara®), Anastrozole (Arimidex®), and Exemestane (Aromasin®), Fulvestrant (Faslodex®), Megestrol Acetate (Megace®) and Androgens (Male Hormones).

Targeted and Biological Therapy

As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes [15]. These targeted drugs work differently from standard chemotherapy drugs [16,17]. They often have different (and less severe) side effects. They are most often used along with chemotherapeutic agents at this time. Trastuzumab (Herceptin®), Pertuzumab (Perjeta™), Lapatinib (Tykerb®), Everolimus (Affinitor®) and Bevacizumab (Avastin®).

Other agents

These agents are not used for breast cancer treatment but used to treat bone metastasis associated with breast cancer.

Bisphosphonates {Pamidronate (Aredia®) and Zoledronic acid (Zometa®) **[18]**, are drugs that are used to help strengthen and reduce the risk of fractures in bones that have been weakened by metastatic breast cancer. Denosumab (Xgeva®, Prolia®) may help other systemic therapies, like hormonal and chemotherapies to work better.

Current Breast Cancer Research and Treatment

Research on the causes, prevention, and treatment of breast cancer is being done in many medical centers worldwide. Current status of research in treatment of breast cancer is given below:

Surgery

Presently more focus towards oncoplastic surgery [19], breast reconstruction surgery and mastectomy. Recently concept of skin, aerola and nipple sparing mastectomy has evolved in which the only the tumor is removed sparing the above mentioned structures which can further help in breast reconstitution surgery.

Radiation therapy

For women who need radiation after breast-conserving surgery, newer techniques such as hypofractionated radiation or accelerated partial breast irradiation may be as effective and offering a more convenient way to receive.

Chemotherapy

Advanced breast cancers are often hard to treat, so researchers are always looking for newer drugs. A drug class has been developed that targets cancers caused by BRCA mutations called as PARP inhibitors [20] and they have shown promise in clinical trials treating breast, ovarian, and prostate cancers that had spread and were resistant to other treatments. Recently, new drug everolimus included in class of mTOR inhibitor was developed which could prove effective in treatment of estrogen positive breast cancer.

Targeted and Biological therapies

Targeted therapies are a group of newer drugs that specifically take advantage of gene changes in cells that cause cancer. Recently, a new drug for patients whose cancer cells have too much HER2 receptors has been approved by the FDA. This drug, ado-trastuzumabemtansine (Kadcyla™) was formerly called TDM-1 [21]. It is made up of the same monoclonal antibody found in trastuzumab attached to a chemotherapy drug known as emtansine (DM-1). In this type of antibody drug conjugate, the antibody acts as a homing device, taking the chemotherapeutic agent directly to the cancer cells. Bevacizumab and several other anti-angiogenesis drugs are being tested in clinical trials. Everolimus (Afinitor) is a targeted therapy drug that seems to help hormonal therapy drugs. It is approved to be given with exemestane (Aromasin) to treat advanced hormone receptor positive breast cancer in post-menopausal women. The epidermal growth factor receptor (EGFR) is another protein which is expressed on the surfaces of many cancer cells. Drugs that targets EGFR mainly comprises monoclonal antibodies (cetuximab and panitumumab) and tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, canertinib) are already in use to treat other cancers, while other anti-EGFR drugs are still considered experimental [22, 23, 24].

Challenges in Development of Therapies for Cancer

Several challenges are involved in the development of therapies for cancer and some of the major ones include narrow therapeutic index of cytotoxic drugs and their nonspecific distribution in the body. To overcome these challenges, researchers are working on two diverse approaches which are enlightening the path in development of effective therapy for cancer. First approach is genomics and proteomics research which is assisting in the identification of new tumor specific molecular targets [25,26] that will aid in the synthesis of 'perfect fit' drug molecule with delicate therapeutic activity and minimum side effects. Second approach involves developing innovative drug delivery systems which include nanoparticles, liposomes, polymersomes, micelles, dendrimers, microemulsion etc. These systems can provide tumor specificity, maintain therapeutic concentration of drug for long periods of time and reduce drug related toxicities. However, these novel drug delivery systems also suffer from one or more drawbacks; specifically, low encapsulation efficiency and poor storage stability of liposomes [27]; limited drug loading capacity and amenability for only small molecules in case of polymersomes and micelles; and small size of dendrimer causing their diffusion into unwanted regions. Proteins nanoparticulate systems have advantages over other novel drug delivery system in treatment of cancer. So, the development of protein nanoparticulate system can be a good option.

Conclusion

The cancer is death leading cause diseases and breast cancer is one them. Many researchers are doing scientific research on the cancer treatment. Surgery, radiography and chemotherapy are the current treatment of cancer but the side effects of this treatment is more. On the other side there are many side effect of these treatment. To overcome such side effects target based therapy treatment is going on with less side effects. These development in cancer will lead the better treatment and future for the world.

Author Contribution

All authors are continuted equally.

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