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Breast Cancer and Chemotherapeutic Drug Resistance: A Treatment Challenge

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ABSTRACT

Breast cancer is a commonly occurring malignancy and leading cause of cancer associated deaths in women globally. It is estimated that 1.7 million new cases (25% of all types of cancers) with 521,900 death in year 2012. There are multiple risk factors associated with breast cancer in women but breast density, genetic tendency, age and estrogen dysregulation are notable. Breast cancer is a heterogeneous ailment caused by common effect of hereditary and ecological variables. Thorough understanding of breast cancer etiology results in the development of molecularly targeted novel therapies. The clinical utility of chemotherapy is based on multiple factors which include tumor size, involvement of lymph node, and presence of hormonal receptors including estrogen, progesterone and HER2. Drug resistance is one of the leading problems in cancer chemotherapy, especially in case of breast cancers. To this end, several ongoing trials are examining novel combinations of drugs that are intended to target key signaling pathways involved in in the progression of disease. These improvements in therapy will potentially overcome drug resistance in breast cancer patients. As well as, identifying other biomarkers and potential drug targets may further lead to develop new chemotherapy combinations that will eventually extend the efficacy of these combine therapies.

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Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy in women and a leading cause of cancer deaths globally, estimated 1.7 million new cases (25% of all types of cancers) with 521,900 death in year 2012 [1] (Figure 1).

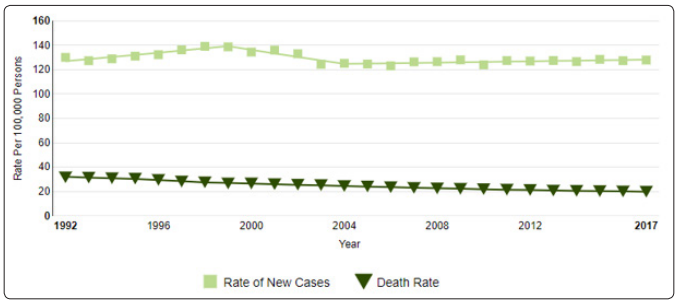

Figure 1: Number of New Cases and Deaths per 100,000. Adapted from https://seer.cancer.gov/statfacts/html/breast.html

It is considered as the second most commonly occurring invasive cancers. Its prevalence is greatly variable over the world with being the lowest in underdeveloped countries like in East Africa 19.4 per 100,000 people and highest in developed countries like 89.7 per 100,000 in West Europe. It affects approximately 12% of women worldwide. Breast cancer was considered to be the most common female malignancy in 2012 when it was found to compromise 25.2% of all malignancies diagnosed in women. In 2008, it caused 458,503 deaths worldwide which comprised 13.7% of all women deaths by cancer. In contrast lung cancer was responsible for 12.8% of women mortalities by cancer the same year. Since the prevalence of breast cancer is higher in women as compare to men, the overall mortalities caused by breast cancer were 6% of all malignancies in men and women compared to 18.2% of all mortalities by cancers. The differences in frequency of cancers worldwide depends upon detection at early stages and diverse risk factors involved in breast cancer. Breast cancer is considered to be the most common and second most shared cause of female cancer based mortalities in United States. [1-9]. According to a study 246,660 new cases of female breast cancer are estimated in 2016, which comprise 14.6% of all novel cases; of which 40,450 people are expected to die from this malignancy. During their life time, about 12.3% of women are expected to diagnose with breast cancer. Women are likely to be more prone to breast cancer than men, in 2015 roughly 2300 men were diagnosed and 440 death were reported due to breast malignancy. The rate of breast cancer incidence are remarkably higher between the ages of 60 to 84 year in white women as compared to black women. However, black women are at higher risk of having breast cancer before the age of 45 years. Frequency of breast cancer related deaths is higher in

non-Hispanic black and white women as compare to other racial and ethnic groups. All through 2004-2012, rate of overall breast cancer incidence remained same in all ethnic groups except Alaska Natives and American Indians where breast cancer cases dropped every year (Figure 2) [9, 10].

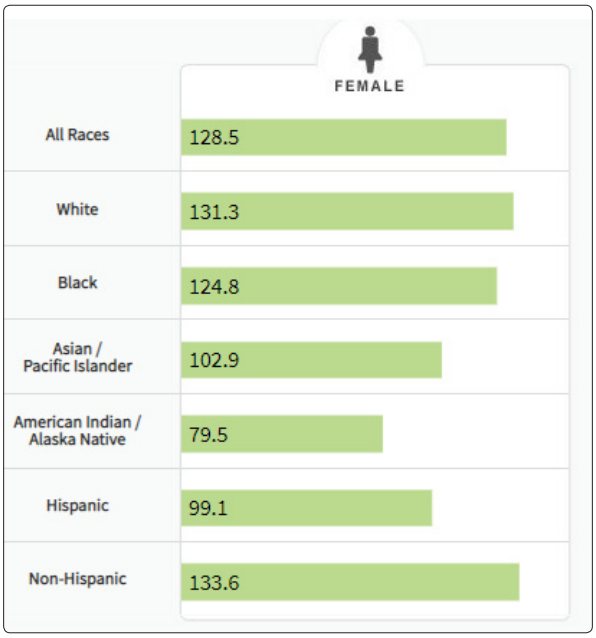

Figure 2: Number of New Cases per 100,000 Persons by Race/ Ethnicity. Adapted from https://seer.cancer.gov/statfacts/html/breast.html

The main reason for this decrease in cases is still not clear but may be it is the result of novel developments in tumor therapies and also the survival rate has improved (Figure 3).

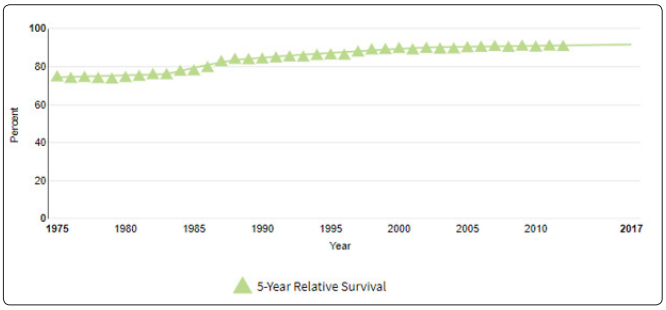

Figure 3: Percent of Cases and 5-Year Relative Survival by Stage at Diagnosis. Adapted from https://seer.cancer.gov/statfacts/html/breast.html, Finally, screening of breast cancer in females at early stages incentivize the debate

Risk Factors Associated with Breast Cancer

Risk stratification of an individual is a significant part for diagnosis of breast malignancy. The estimated risk of an individual can affect both patient preferences along with recommendation for screenings. Multiple risk factors are associated with breast cancer, like genetic tendency, age and estrogen dysregulation. On the other hand, breast density is also considered to be a significant risk factor. Except some genetic alterations such as BRCA, the risk factor is relatively small but may have impact on each other. Breast cancer is mainly a heterogeneous disease caused by hereditary and ecological factors. Epidemiological studies confirms the contiguity of risk factors includes, age, obesity, use of alcohol and estrogen dysregulation, but family history is the most important risk factor of breast cancer. It is reported that 20% of all breast malignancies have family history behind them. In United States, risk for malignant breast tumor at age of 40, 50 and 60 year is correspondingly, 1.5%, 2.3%, and 3.5% [11-18]. Different hormonal levels influence the risk of developing breast cancer in women. High level of endogenous estrogen may increase the risk for pre and post-menopausal females [14]. Other common risk factors include breast tissue radiotherapy, Obesity, drinking alcohol, given birth to an older age or not even given a birth, delayed menopause, up taking different hormones (estrogen and progesterone) to avoid signs of menopause, appearance of dense breast tissue on mammogram, family history of breast cancer (first-degree relatives), personal history of having benign breast growths or invasive breast cancer, ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), smoking, breast feeding, oral contraceptives and diet.

Molecular Classification of Breast Cancer

On the basis of molecular or gene expression profiling, breast cancer is different and divided into three different sub types includes Luminal, human epidermal growth factor receptor 2+ (HER2+) and basal breast like breast tumors. Each type behave differently in accordance with treatment response, disease progression risk, and organ selection for metastasis of tumor. The luminal tumors are estrogen and progesterone receptor positive (ER/PR+) and majority of these tumors respond effectively against hormone based therapies, however HER2+ tumors has overexpression of an oncogene ERBB2 which could be controlled efficiently by using different approaches to anti-HER2 therapies. On the other hand, basal like tumors lack hormone receptors and HER2; thus, majority of these tumors classified as triple negative breast cancer (TNBC). Currently there is no such targeted molecular therapies available for these tumors and unfortunately they respond less than 20% to standard available chemotherapeutic agents. Several studies hypothesized the inter tumor heterogeneity and its origin in breast cancers. Accordingly, luminal lineages are committed progenitors of luminal and HER2+ based tumors, whereas basal like tumors originate from differentiated stem like cells. However pattern of gene expression and experimental evidence suggests that following genetic and epigenetic factors luminal progenitors may serve as precursors for basal like tumors [19-25].

The Heterogeneity of Breast Cancer

Before the introduction of modern molecular profiling techniques, morphological observations recognized that breast cancer is not a simple disease but a heterogeneous malignancy. It was classified on the basis of multiple factors including the grade of tumors, status of lymph node, presence of predictable markers such as estrogen receptor (ER) and lately, human epidermal growth factor receptor 2 (HER2). The heterogeneity of breast cancer was also proved by the molecular profiling with the help of DNA microarray data analysis. The demonstration was done on the basis of genetic and immunohistochemical expression of ER, PR and HER2 breast cancer and was further divided into five clinical sub groups: luminal A, luminal B, HER2, basal and normal breast cancer.

Targeted Therapies against Breast Cancer

A deep understanding of etiology of breast cancer leads towards the identification of multiple molecular targets which results in development of novel therapies. The tyrosine kinase inhibitors (TKIs) targets at various hormonal sites including (HER1, HER2, HER3 IGF receptor [IGFR] and FGF receptor [FGFR]), Intracellular pathway inhibitors (PI3K, ERK, AKT and mTOR), inhibitors of angiogenesis and certain agents which interfere with DNA repair mechanism. Some of these inhibitors shown remarkable activity and are being effectively used in treatment of

breast cancer, for example lapatinib, transtuzumab and anti-HER2 agents). Transtuzumab is a monoclonal antibody as has proven the most effective therapy in the women having HER2+ breast tumors. Another promising agent lapatinib, a dual inhibitor of EFGR;HER1 and HER2, bevacizumab a monoclonal antibody targets vascular endothelial growth factor (VEGF) has the greater efficacy against multiple types of breast tumors [26, 32].

The Estrogen Paradox

To treat ER+ breast cancers it is necessary to target ER itself. There are two ways to treat this either by using certain anti-estrogen tamoxifen or by suppressing the ligands (estrogen) available for the receptor. Due to their proven activity these endocrine therapies are widely used to treat early or recurrent and metastatic breast cancer. Taking in consideration with the risk factors of breast cancer it is indicated that it is an estrogen based malignancy. However as a disease breast cancer is not appeared until women's body has depleted estrogen secretion. The peak age for occurrence of this disease is 62 years which is nearly 10 years after menopause. Less than 5% of total breast cancers arises under the age of 50 when estrogen levels are highest. Several hypothesis may be articulated to elucidate this absurdity [33-35]. Each menstrual cycle is a probability to start proliferation in compartments of mammary epithelial cells with an opportunity for genetic and epigenetic errors (Overexpression of oncogenes and methylation of tumor suppressor genes) the possibility of which increased with every proliferative cycle. Further defects in DNA repair system (mutations in BRCA or p53) also enhances the likelihood of getting breast cancer [34].

Chemotherapy

The advantage of chemotherapy depends upon multiple factors which include tumor size, involvement of lymph node, and presence of hormonal receptors (Estrogen and progesterone) and overexpression of HER2 in cancer cells. It is indicated that TNBCs and HER2+ breast cancers are more sensitive to chemotherapy than HR+ breast tumors. Certain gene expression panels (PAM 50, Oncotype DX and Mammaprint) are the tests to evaluate the risk of recurrence at early stage of HR+, HER2- breast tumors. Those factors potentially identify the candidates who would benefit from chemotherapy, in addition to those who could safely escape. In United States, Oncotype DX 21-Gene Recurrence Score is widely used. The DX 21-gene high score identifies those who would likely benefit from adjuvants chemotherapy along with hormone therapy where as low score tells those who could safely avoid. The following scores are totally independent of patient's age and size of the tumor. In multiple studies researches concluded that combination of two or more drugs work more effectively on breast tumors at early stage than single drug. Depending upon the chemistry of drugs, adjuvants and neoadjuvant therapy usually continues for 3-6 months. If interruption or significant delays could be avoided, the combine therapy is very effective when dose and cycles of drugs completed on time. Further, general principles have been established for the guidance of oncologist to select when and which type of therapy could be used. The decision to give chemotherapy should be made by looking the characteristics of the cancer (HR, HER2 status, stage of the cancer, grade and lymphovascular invasions) and factors associated with patient (likely benefits, potential toxicity, life expectancy, age and patients preference). Multiple studies suggested the benefit of polychemotherapy over monochemotherapy. The use of anthracyclines become part of standard care but a greater risk of cardiac toxicity is involved, on the other hand long lasting benefits of taxanes should overweigh their risk of long lasting neuropathy [36-41].

Chemotherapeutic Drug Resistance

Drug resistance is one of the leading problems in cancer chemotherapy, especially in case of breast cancers. The higher motility rate is the indication that chemotherapy yet not overcome the disease. The problems in chemotherapy amplified since emergence of drug resistance in case of breast cancer. Generally, resistance has two categories, first poor drug delivery to cancer cells resulting in poor absorption of drug, increased excretion, increased drug metabolism results lower levels of drugs in blood stream and ultimately reduced availability of drugs to the tumor tissue. Secondly the epigenetic changes due to which drug sensitivity is effected. These epigenetic changes, include DNA methylation, nucleosome remodeling and histone deacetylation . These epigenetic changes leads to the tumor suppressor gene silencing. Some other alterations lead to the reactivation of oncogenes and interfere with apoptotic and growth regulatory pathways. However, these modifications are sometimes reversible, like adding specific inhibitors can revert the process. Different mechanisms of drug resistance have been suggested including alteration in drug transport, drug targets, drug metabolism, drug-detoxifying mechanisms, enhanced DNA repair and deregulation of apoptotic pathways. Additionally, some monolayer cells which are sensitive to drug in cell culture, becomes resistant when transplanted to animal models [42-52]. This is the indication that tumor geometry, extracellular matrix or other environmental factors are involved in drug resistance. In cell culture, cells growing in three-dimensional (3D) shape, imitating in vivo geometry may contribute to the drug resistance [43, 52, 53]. In cell culture, cancer cells become easily resistant to a single agent or a group of agents showing the similar mechanism of actions, by altering the repair of drug induced damage to DNA or by increasing DNA repair mechanism. After resistance to single agent cell might show cross-resistance to other mechanistically or structurally different class of drugs. This phenomenon is known as multidrug resistance. Resistance to some natural or hydrophobic drugs also called as classical multidrug resistance mainly results from expression of ATP-dependent efflux pumps belongs to ATP-binding cassette (ABC) transporter family that share sequential and structural homology. Anthracyclines; doxorubicin and daunorubicin, vinca alkaloids; vinblastine and vincristine, drugs for stabilization of microtubules; Paclitaxel, inhibitors of RNA-transcription actinomycin-D, all are the drugs which are affected by multidrug resistance. Increased expression of a protein called P-glycoprotein (P-glycoprotein) is among the prominent mechanisms of multidrug resistance [54, 57]. Pgp is membrane associated glycoprotein of up to 170-kDa that may extrude several cytotoxic compounds including doxorubicin from cytoplasm to outside of cell, thus reducing the cellular drug concentration [42].

Conclusion and Future Directions

Over the past century, the use of multiple approaches took benefit of the advancement of our understanding of the etiology of breast cancer. Each strategy is based upon one of the many aspects of this disease; however not a single strategy is suitable to treat all types of cancers. By the time we moved from the strategy of totally eradicating the cancers to induce long term inactivity of the cells. This tactic could be as equivalent of a therapy because patient lives till their natural end without a deterioration of cancer by avoiding the wakening of dormancy. Several alteration are required by the breast cancer to initiate and progress in the body. These changes include (1) strong estrogen drive and/or (2) various genetic and epigenetic changes, (3) Feeble immune surveillance and chronic inflammatory milieu (4) damage to intracellular regulatory mechanism (5) significant decrease in apoptosis and (6) lenient microenvironment. Inherited factors act as a magnifier of

the preceding turbulences. The interpatient heterogeneity depends on diverse risk factors and patient's response to a particular treatment. Multiple host dependent factors and used treatments contributes to constant evolutionary stress which is accountable for intrapatient heterogeneity and clonal evolution. Inter and intrapatient heterogeneity is considered to be one of the principal challenge to cure breast tumor. Genomic tools contributed on very large scale for selection of specific treatment for individual patients which helps to reduce treatment related morbidity and mortality. Nevertheless the improvement of biomarkers and diagnostic tools is still needed to enhance our assessment to forecast the benefits from existing therapies. Chemotherapy of the patient helps to induce DNA damage or arrest the cell cycle. However current regimens are more effective and reported to have less cellular toxicity against normal cells than the old one. Over the past decade, advancement in chemotherapies seems to have plateaued with lack of novel or major advancements. Unfortunately, drug resistance is one of the active barrier to existing therapies against breast cancer. The mechanism of drug resistance decreases the therapeutic efficiency of any anticancer drug, especially in patients already exhausted by multiple options. Though it is hoped that gene profiling can assist to select suitable patients for precise treatment, progression of drug resistance is a key restraint. To this end several ongoing future trials are examining new effective combinations intended to target notorious pathways involved in cell signaling that are active in progression of disease. These improvements in therapy will continue to overcome drug resistance and progression of disease in any breast cancer patient. Identifying other biomarkers and potential drug targets may further leads to the progression of new chemotherapy combinations that will eventually extend the efficacy of these combine therapies. Further research on these molecular targets can be proposes for the therapeutic interventions of breast cancer.

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