Research Article

Tactics of Breast Cancer Therapeutics and Future Outlooks

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Abstract

The breast cancer is a disease in which malignant cells form in the tissues of the breast and leading to death among the woman in worldwide. Early detection of breast cancer is a challenging to the breast cancer therapeutics, because of the different patterns of the breast cancers includes, Hormone receptor-positive (ER+ and/or PR+), Receptor HER2-positive; and Triple-negative breast cancer (TNBCs) types. These ER+, PR+ and HER2+ marker proteins also serve as breast cancer therapeutic targets of specific therapeutics. Tumors with none of these ER-, PR-, HER2- are known as TNBCs. In this review, the author deliberated the current status, different types of breast cancers, risk factors associated with breast cancers, treatment strategies, and side effects of the breast cancer treatments. At the end of this review overall future outlook of the breast cancer treatments and its future nanoparticles, peptides and PROTACs - based therapeutic approaches are well discussed.

ABBREVIATIONS


INTRODUCTION

At present, breast cancer is reached as the most commonly diagnosed cancer with an estimated amount of 1.7 million cases and over 520,000 deaths worldwide [1]. It accounts of all other cancer types and 15% of all cancer related deaths in females. The majority of breast cancers are sporadic rather than inherited. Many environmental risk factors account for a greater number of breast cancers. Studies also estimate that 12-30% breast cancers have a heritable genetic component. Only, 5-10% of breast cancers are related to inheritance of major autosomal dominant predisposition gene [2]. Breast cancer is the first cause of death for malignancy in the female. Breast cancer is the malignant tumor arising from the cells of the breast and it predominantly occurs in women. In 2017, invasive breast cancer will be diagnosed in about 252710 women. Breast cancer also leads to increased physical and mental distress.

The research focused on breast cancer is being increasing recently with involving many aspects, which are including the cause of disease, treatments strategies (surgery, radiotherapy, chemotherapy), gene research, nano medicine research and so on. The advanced technology based on targeting breast cancer research has rapidly developed especially in recent years [3]. Furthermore, the identification of new target molecules to the breast cancer and use of multifunctional combination therapies might have improved the understanding the pathways which leads to emergence of mechanism of resistance such as multidrug resistance (MDR), however, subtypes breast cancer like TNBCs seems to exploit different alternative proliferative pathways which are not yet fully understood and necessary attentions and elucidation. Therefore, targeted breast cancer therapy, which optimizes the accuracy of antitumor activity efficacy and minimizes the toxicity to normal tissues, plays a crucial role in breast cancer treatment in the new era of advanced precision medicine. The next generation therapy, in vivo cells are arranged in three-dimensional (3D) structures and not attached to planar surfaces. In vitro 3D cultures provide an additional step that can bridge the gap between conventional 2D culture and animal models. In vitro 3D cultures enable a better understanding of the molecular and cellular mechanisms, which are more relevant to animal and human studies, thus facilitating the development and screening of new drugs. Therefore, this 3D in vitro breast tumor model research allows to recreate or modify their drug designs prior to initiating expensive, time-consuming animal experiments.
MOLEolarly categorized breast cancer types

Breast cancer is categorized on the basis of the molecular existence of estrogen receptor (ER) positive, the over amplification of HER2/ErbB2 gene and the absence of these three nuclear receptors likely ER, progesterone receptor (PR) and HER2/ERBB2 (Triple Negative) [3, 4]. Amongst, while for the first two groups of breast cancer types are receptor-specific therapy is applied, however chemotherapy remains the mainstay of treatment for triple negative breast cancer. It is a group of heterogeneous diseases characterized by different molecular based subtypes and responses to treatments. In current research settings, the aforementioned breast cancers types are classified as luminal A, luminal B, HER2-enriched, and basal-like, based on their molecular subtypes [5]. However, based on treatment options, breast cancers are roughly divided into three groups.

Figure 1:
(i) Hormone receptor-positive (ER+ and/or PR+)
(ii) Receptor HER2-positive; and
(iii) Triple-negative (ER-, PR-, HER2-)

RISK FACTORS OF BREAST CANCER

The major risk factors which are associated with breast cancer including alcohol consumption, taking estrogen-containing products such as birth control pills, all increased the estrogen lifetime exposure including early menarche and late menopause, low intake of fruits and vegetables, obesity, exposure to radiation, and sedentary lifestyle [6]. Other, ageing is also a risk factor in that moreover 80% of women with a breast cancer diagnosis are older than 50 years. Family history of breast cancer and certain mutations, such as BRCA1, BRCA2, and p53, increase the high risk for breast cancer [7]. Furthermore, high density of breast has also been shown to be a strongly independent risk factor for breast cancer. It has been reported that women with a high breast density compared to women with a low breast density have a four-to-six fold increased risk of developing the disease. Pre-menopausal women are known to have a higher proportion of dense breast tissue, as breast density decreases with age. Then, obesity has shown to increase the risk factors of several types of different cancer in women, such as post menopausal breast cancer [8]. However, obesity in younger women has been reduce the risk of breast cancer [9]. However, understanding the breast cancer risk factors can lead to early detection and healthier lifestyles in future (Figure 2).

STRATEGIES OF BREAST CANCER DETECTION

Detection of breast cancer early is the state-of-the-art of cancer treatment, is the most important strategies to prevent breast cancer deaths. Breast cancer detection in early will have not spread, is easier to treatment successfully. Regular screening detection test is the most reliable way to find breast cancer early. As per the American Cancer Society has given the screening guidelines for women at average risk of breast cancer, and for those at high risk for breast cancer. Breast cancer detection involves the self and clinical examination and radiography which are including mammography positron emission tomography and magnetic resonance imaging followed by invasive biopsy for the histological confirmation of invasive disease [10]. The development of mammography has been greatly increased the likelihood of early detection of breast cancer, and randomized clinical trials have demonstrated a 30% reduction in breast cancer mortality in women age 50-69, who are screened annually with mammography [11]. Different types of tests that could be used to diagnose the breast cancer screening test such as mammograms, breast ultrasound, breast MRI scans, newer and experimental breast imaging tests. Although early detection of breast cancer by mammography is associated with less invasive surgical procedures and may increase survival, the 5-year survival rate of metastatic breast cancer (stage IV) is still below 15%. Thus, the development of effective therapies against invasive breast cancer and particularly highly metastatic disease still remains a significant priority. The treatment of primary breast cancer has mainly relied upon initial surgical intervention (including lumpectomy, or partial or total mastectomy) followed by radiation and various forms of systemic adjuvant therapy including cytotoxic chemotherapy, hormonal therapy, and most recently immunotherapy (e.g. trastuzumab) [12].

Over the past 30 years, many novel drugs have been developed for controlling breast cancer growth, and these drugs have shown significant clinical benefits in some cases of breast cancer. Approximately 65%of breast tumors demonstrate hormone receptor positivity and therefore the most common breast cancer therapies today are hormonal therapies e.g. selective estrogen receptor modulators (SERMs), and aromatase inhibitors [13]. Additional therapies include chemotherapy (e.g. anthracyclines and taxanes), often used in combinations, immunotherapies (e.g. trastuzumab) and nano-therapy (Figure 3) [14, 15]. The potential applications of different kinds of nano materials utilized for the treatment of breast cancer is well-established and described in detail with conjugation with biomolecules, such as antibodies, proteins and oligonucleotides (Figure 3).

CONVENTIONAL BREAST CANCER THERAPY

Based on the conventional breast cancer treatment the following therapies are given such as hormone therapy, immunotherapy, radiation therapy. However, recent advances in new drug designing for the breast cancer have led to the development of new small molecular weight chemotherapeutic agents, peptides, proteins, and nucleic acid molecules that can be used for the delivery to the breast cancer therapy.

Breast Cancer Hormone Therapy

Estrogen receptors (ER) are well-known to regulate breast cell growth in response to the estrogen. The estrogen-dependent breast cancer growth was first demonstrated by the fact that a removal of the ovaries of premenopausal women was associated with the regression of advanced breast tumors [16]. ER is a transcription factor that belongs to a member of the nuclear hormone receptors super family, which initiates or enhances the transcription of genes containing specific hormone response elements (estrogen response element, ERE) [17]. The human ER protein has a molecular weight of 66 kDa and consists of 595 amino acids that form six different functional domains, including a ligand binding domain for estrogen and a DNA
Figure 1 The classification of clinical breast cancer types and their percentage level in each.

Figure 2 The major breast cancer risk factors and its different conditions are can be control and cannot control.

Figure 3 Based on the risk factors and prevention of breast cancer the screening, chemo and biological prevention methods are described. (Copyright permission 2017 from Ivy spring International Publisher). Basic functional structure and ligands of nanoparticles used in breast cancer diagnostics and treatment. (Copyright permission 2017 from Ivy spring International Publisher and Future Medicine Ltd).

binding domain. Estrogen, a ligand for ER, is produced by the ovary, diffuses through the plasma membranes of cells where it binds to the ER (Figure 4).

Once the ER binds estrogen, it dimerizes, translocates to the nucleus, and binds to ERE in the promoter region of genes, thereby activating downstream gene expression. Selective estrogen receptor modulators, SERMs (tamoxifen, raloxifene, andarzoxifene) have been established to antagonize the effects of ER activation through the AF2 domain [13]. Among all breast cancer cases, hormone receptor positive breast cancer accounts for 75%, and hormonal therapy has been shown to significantly reduce the risk of breast cancer recurrence and increase the 10-year survival of women with ER+ breast tumors. Five years of adjuvant tamoxifen treatment reduces the annual breast cancer death rate by 31%.
Breast Cancer Immunotherapy

Human epidermal growth factor receptor 2, a receptor tyrosine kinase, is upregulated in 25% of breast tumor due to abnormal gene amplification and over expression of which clinically correlates with reduced survival and reduced time to relapse compared to patients with normal receptor levels [18-20].

The Her2 dimerization is essential for an activation of signaling cascade to promote cell survival through the Ras-Raf-mitogen-activated protein kinase-extracellular-signal-regulated kinase (ERK) kinase (MEK)/ERK pathway. These findings led to the development of trastuzumab (anti-Her2 Mab; Herceptin®, Genentech), the first genomic research-based, targeted anti-kinase therapy approved by the Food and Drug Administration (FDA approved in 1998) for the treatment of patients with invasive breast cancers over-expressing Her2 [18]. Trastuzumab binds to the extracellular membrane domain of Her2 and inhibits the proliferation and survival of Her2-dependent tumors by blocking the dimer formation (Figure 5). In a phase III comparison trial in which trastuzumab was added to first-line therapy with anthracycline-cyclophosphamide or paclitaxel for patients with Her2+ metastatic breast cancer, the addition of trastuzumab provided significantly better results (25.1 months median survival) than standard therapy alone (20.3 months median survival), with a 20% overall survival improvement.

Systemic Breast Cancer Radio-Chemotherapy

Most of the breast cancer radiation therapy is administered by a radiation oncologist at a radiation center and usually begins three to four weeks after surgery. The radiation is used to destroy undetectable cancer cells and reduce the risk of cancer recurring in the affected breast [21]. There are two main kinds of radiation therapy that may be considered, and some people have both. External Beam Breast Cancer Radiation (Traditional cancer-killing rays delivered by a large machine), and Internal Breast Cancer Radiation (Newer treatments that inject radioactive cancer-killing treatments only in the affected area) (Figure 6).

The triple negative breast cancer is highly proliferative and aggressive with poor prognosis due to a lack of specific treatment guidelines, and therefore, triple-negative breast cancers are managed with standard radiotherapy and chemotherapy. Unfortunately, such treatment is associated with high rates of local and systemic recurrence. Many cytotoxic agents (such as cyclophosphamide, 5-fluorouracil, doxorubicin, taxanes, capcitabine), either as single agents or in combination regimens, have demonstrated activity against advanced breast cancer. Large prospective clinical studies have clearly demonstrated that the hormone and/or immune therapy greatly reduce the mortality of patients with ER+/HER2 or PR+/HER2 breast cancer, a group that comprises 75% and 15–20% of breast cancer cases, respectively. However, the remaining 10–15% of breast cancers comprise a "receptor-negative" or "triple-negative" category defined by the absence of expression of these three receptor proteins [22].

The most commonly used non anthracycline-based regimens cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) have objective response rates of 50–70%, with a median duration of response of 10–12 months. More recently, single agent Capecitabine has shown activity in advanced disease and superiority to CMF regimens in patients with metastatic breast cancer. Taxanes (e.g. paclitaxel and docetaxel) are among the most effective and currently used cytotoxic agents combined with nanoparticles in breast cancer [23]. The combination docetaxel/capcitabine has shown survival advantages when compared to single agent docetaxel suggesting that the combination regimen may show a superior benefit.

SIDE EFFECTS OF BREAST CANCER THERAPY

Breast cancers treated with a combination chemotherapy strategy with the common addition of biological agents that demonstrate synergistic or additive effects by multiple mechanisms. Even though chemo and adjuvant therapies have proven their efficacy as discussed above, however, side effects are associated with these therapies are the serious and sometimes even life threatening [24]. The known side effects of chemotherapy are caused by the cell killing effect of such agents. This derives from the fundamental phenomenon that available cytotoxic agents are not selective in their activity, and therefore non-specifically damage normal replicating cells in the bone marrow, gastrointestinal epithelia, and hair follicles. After
treatment with trastuzumab the women develop heart related problems during the pertuzumab, or trastuzumab emtansine can lead to congestive heart failure.

For example, acute toxicities associated with conventional doxorubicin (Dox) include myelosuppression, nausea, vomiting, mucositis, and alopecia [25]. The most serious, conventional doxorubicin-induced toxicity is irreversible congestive heart failure. Tamoxifen is also associated with serious side effects and complications including an increased risk for endometrial cancer by 2.4 times in women aged 50 years or older and thromboembolic disease by 1.9 times. Targeted therapies showed significantly positive effect as evidenced by multiple clinical studies, however, even these targeted therapies caused serious side effects. Trastuzumab alone or in combination with chemotherapy may cause serious heart problems including ventricular dysfunction and congestive heart failure in addition to common flu-like symptoms. Therefore, the development of a novel treatment strategy including selective delivery of cytotoxic agents to tumor mass for the treatment of advanced breast cancer is critical to improving the therapeutic index and efficacy/toxicity balance.

FUTURE OUTLOOKS

Application of nanotechnology to medical science has been emerging as a new field of interdisciplinary research in medicine and is expected to bring a breakthrough to address unsolved medical issues. Nanoparticles drug delivery system (NDDS) for the therapeutic delivery systems can be used to deliver therapeutic entities such as small molecule drugs, peptides, proteins and nucleic acids either as single agents or as multiplexed combinations [26]. Increasing evidence indicates that the selective delivery of nanoparticle therapeutic agents into a tumor mass could minimize toxicity to normal tissues and maximize bioavailability and cell killing. These advantages are mainly attributed to changes in drug tissue distribution and pharmacokinetics. Furthermore, it has been demonstrated that nanoparticles can escape from the vasculature through the leaky endothelial tissue that surrounds the tumor and can accumulate in certain solid tumors via the EPR effect [27]. After escaping from the vessel, non-targeted nanoparticles will typically be cleared from the tumor sites due to their lack of cellular uptake. In contrast, tumor-targeted nanoparticles can enter tumor cells from the extracellular space via receptor-mediated internalization. A variety of tumor targeting ligands, such as antibodies, growth factors, and cytokines have been used to facilitate the uptake of carriers into target cells. Tremendous progress has been made for tumor-targeted nano therapeutics. The author of this review has reported that conjugation of trastuzumab antibody against the Her2 receptor to nanoparticles comprised of polymer has been described as a successful way to increase intracellular uptake by cells over expressing Her2 via receptor-mediated
endocytosis for breast cancer targeted therapy (Figure 7) [28, 29]. Nanotechnology has already provided significant advantages in several areas of medicine as discussed, and nanotechnology-based therapeutics for breast cancer treatment (Doxil® and Abraxane®). While basic and clinical science have revealed and identified multiple problems that cause a reduction of therapeutic efficacy of systemic chemo and immunotherapy for breast cancer, numerous new nanotechnology-based drug delivery platforms have been tested to address these unmet clinical problems.

Peptide targeted breast cancer therapy proposed that cell-permeable peptide inhibitor ERAP regulates multiple ER α-signalling pathways associated with tamoxifen resistance breast cancer cells by inhibiting the BIG3 and PHB2 interaction [30]. Intrinsic PHB2 released from BIG3 by ERAP directly binds to both nuclear- and membrane-associated ER α, which leads to the inhibition of multiple ER α-signalling pathways, including genomic and non-genomic ER α activation and ER α-phosphorylation, and the growth of ER α-positive breast cancer cells both in vitro and in vivo. Therefore, inhibiting the BIG3 and PHB2 interaction a new therapeutic strategy for the treatment of luminal-type breast cancer therapy (Figure 7).

Protac - Proteolysis Targeting Chimeric Molecule is also a new technology is to create a chimeric molecule that bridges any cancer-causing protein to an E3 ligase for subsequent ubiquitination and degradation [31]. Protasis consist of one moiety, e.g. a peptide, which is recognized by the E3 ligase. This moiety is then chemically and covalently linked to a small molecule or a protein that recognizes the target protein (Figure 7).

TNBCs types constitute of a heterogeneous subtype of breast cancers that have a poor clinical outcome and no approved targeted therapy is available, moreover, efforts have been revealed promising molecular targets [32, 33]. Different potential therapeutic options in TNBCs are summarized in Figure 8. Breast cancer resistance mechanisms in targeted therapies represents the main challenges in research also clinic; the advanced combination of different molecules used to target different levels of signaling pathways by synergistically blocking the breast cancer cell escape directions and minimizing the emergence of survival mechanisms, could prove to be a promising way to forwarding nest generation breast cancer therapy, that specific molecular targeting particularly for metastatic relapses should be carried out to elucidate further resistance phenotypes and allow for the design of specific new breast cancer targets.

It is evident that anti-cancer therapy certainly needs a breakthrough to eradicate breast cancer related death. Nanotechnology is one of the greatest fields in medical science with a promise to address long issues. There are an overwhelming number of distinct nanoparticles that have been developed which

![Figure 7](image_url) Breast cancer therapeutics based on nano-based drug delivery system to target her2 expressed breast cancer targeted therapy. (copyright permission from ref. 28 American Chemical Society-2014). Molecular mechanisms of suppression of breast cancer cell growth to novel peptide targeted therapeutic strategies. (copyright permission from ref. 30 Nature Publishing Group-2013). Protac-the common molecular mechanism of theoretically target any abnormal breast cancer protein for ubiquitination and degradation. The protein is recruited to the SCFβ-TRCP E3 ubiquitin ligase, resulting in destruction of the breast cancer protein target.

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vary with respect to many properties, such as particle size, shape, charge, surface modification, and drug payload/therapeutic effect. The future challenges in the successful clinical applications of nanotechnology-based drug delivery are not the lack of novel technologies; it is rather the need to identify favorable physiochemical properties that to overcome multiple barriers. Hence, the present review taken and written as a challenge against the breast cancer therapy.

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