Selection and Application of Targeted Therapy in Breast Cancer

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Abstract. Breast cancer remains a major global health problem, with high mortality and morbidity rates among women worldwide. Breast cancer has diverse molecular and genetic characteristics and therefore requires personalized treatment strategies to improve patient prognosis. Targeted therapies have become the cornerstone of breast cancer treatment, targeting molecular signaling pathways and receptors involved in tumor growth and progression. The present state of targeted treatment for breast cancer, encompassing the disease's triple-negative (TNBC), human epidermal growth factor receptor 2-positive (HER2+), and hormone receptor-positive (HR+) subtypes, is thoroughly reviewed in this article. We'll go over the reasoning for choosing targeted treatments (such tyrosine kinase inhibitors, PARP inhibitors, and monoclonal antibodies) in light of tumor-specific indicators and genetic changes. In addition, the clinical use of these therapies is analyzed, focusing on their integration with treatment regimens, impact on survival, and management of treatment-related side effects. The review also emphasizes the growing importance of biomarkers to guide therapy decisions, the importance of targeted therapeutic resistance mechanisms, and the potential for novel drugs and combination therapies.

Keywords: Breast cancer; HER2+; HR+; BRCA.

1. Introduction

One of the most prevalent malignant tumors in women is breast cancer, accounting for 7-10% of all malignant tumors. Breast cancer can be caused by various factors such as hereditary factors, family history, history of breast disease, each individual is different like gender, hormone levels, dietary habits, obesity, etc. Age also affects the incidence of breast cancer. Treatment options vary from person to person depending on their condition. Each person's tumor size, location, grade, and personal health status affects the choice of treatment. Breast cancer is a very diverse polyclonal illness, despite the fact that studies have demonstrated the high significance of classical biomarkers in this diagnosis. The geographical and temporal progression of malignancies is not entirely captured by tissue-based biomarkers, particularly when the tumors are subjected to various treatments. Furthermore, because tissue-based serial biopsies are invasive and might include sampling mistakes, they present a challenge in the search for biomarkers.

Surgical resection, radiation therapy, chemotherapy, targeted therapy, and hormone therapy are among the current therapeutic options. Targeted therapy aspect is a type of treatment that targets specific molecular targets of tumor cells. Different from anti-tumor therapy and chemotherapy, targeted therapy for breast cancer only works on breast cancer cells and does not work on cells without targets and normal cells, with strong specificity and small adverse reactions. By examining the selection and application of targeted therapies in detail, this review aims to inform clinical practice and contribute to continued advances in breast cancer treatment.

2. HER2-positive (HER2+) Breast Cancer

HER2-positive (HER2+) breast cancer is a highly heterogeneous and complex disease that accounts for 10-20% of all breast tumors. It is characterized by amplification of the ERBB2/HER2 gene and/or overexpression of the corresponding kinase receptor proteins, resulting in tumors that exhibit greater aggressiveness and reduced disease-free survival (DFS) and overall survival (OS). First, HER2+ tumors can be identified in all known intrinsic molecular subtypes. Second, HER2+

tumors demonstrate a wide range of DNA changes, with ERBB2 mutations and alterations in the PI3K/Akt/mTOR pathway being the most common, and these alterations may predict a strong therapeutic response to pan-HER, PI3K, and mTOR inhibitors. In addition, HER2+ tumors are usually accompanied by lymphocyte infiltration, and these tumor-infiltrating lymphocytes (TILs) are predictive of response to neoadjuvant-based HER2-targeted therapies and serve as prognostic indicators.

The availability of humanized anti-HER2 monoclonal antibody trastuzumab into clinical practice and the ensuing emergence of many other anti-HER2-targeted medications (e.g., lapatinib, patuximab, and T-DM1) have reduced the risk of early disease recurrence and/or significantly improved survival in metastatic patients. However, approximately 4%-23% of patients with limited disease will still relapse and metastasize after receiving HER2-based (neo) adjuvant regimens. When the disease progresses to systemic level, it remains difficult to cure at this time [1]. Survival rates for patients with HER2-positive early breast cancer (EBC) treated with chemotherapy and dual antibodies now exceed 90%. Further proof that most individuals with early stage disease have been cured comes from the fact that over half of patients with metastatic HER2-positive breast cancer are diagnosed with de novo disease [2].

Trastuzumab (Herceptin®, manufactured by Genentech in the United States and Hoffmann-La Roche in Switzerland) is a humanized IgG1 class monoclonal antibody that inhibits activity within the HER2 signaling pathway by binding to the extracellular structural domain (ECD) of the HER2 transmembrane receptor, causing cell cycle arrest and facilitating the cellular cytotoxicity caused by antibodies-dependent cell (ADCC).[2] It is the first targeted treatment drug for breast cancer approved worldwide, and a longer response duration (median, 9.1 vs 6.1 months; $p < 0.001$) have all been linked to combinations of trastuzumab with other agents. The pertinent study's findings demonstrated that patients with advanced breast cancer had a 10-month median survival time and a decreased death and recurrence rate when treated with trastuzumab for a year following surgery. HER2 receptor extracellular structural domain (ECD) binding is how trastuzumab binds to the HER2 receptor and causes its anticancer effects. This method of action involves inhibiting antibody-dependent cell-mediated cellular cytotoxicity (ADCC) and ligand-independent HER2 receptor dimerization. When used in conjunction with chemotherapy, trastuzumab improves survival endpoints and quality of life for patients with advanced HER2-positive breast cancer. It is a target for the treatment of early-stage HER2-positive breast cancer [3]. However, this drug has some cardiotoxicity, which leads to the clinical application rate of this drug is not high.

The humanized recombinant monoclonal antibody Pertuzumab (Perjeta), which is produced by Hoffman-Roche in Switzerland and Genentech® in the United States, interferes with the ligand-dependent HER3-mediated signaling pathway and prevents HER2 from heterodimerizing with HER3. Patuzumab has relatively little anti-HER2 occupation when used alone, but when paired with trastuzumab, it may have synergistic benefits. Clinical studies have effectively established the effectiveness of Patuximab in HER2-positive metastatic illness [3].It is less toxic and has no cardiotoxicity, but adverse reactions such as diarrhea can occur in patients treated with the drug.

Cancer vaccines against HER2 and acquired immunotherapy are considered key strategies for the treatment of HER2-positive breast cancer. Cancer vaccines work by inducing CD8 and CD4 T cells to respond to antigens unique to tumors, which in turn stimulates the patient's immune system to identify and eliminate tumor cells [2]. This covers vaccinations that deliver HER2 via viral vectors, plasmid DNA-based vaccines, and vaccines based on the HER2 peptide. An initial clinical trial used plasmid vectors of HER2 protein-coding DNA, plus low-dose GM-CSF and IL-2, in HER2-positive mBC patients who also received trastuzumab. The outcomes demonstrated that the inoculation elicited long-lasting humoral and cellular immune responses against HER2 proteins and was well tolerated. Following vaccination with HER2-targeted vaccines, patients may have mediated delayed hypersensitivity and robust CD8+ cell-specific responses. The effectiveness and longevity of T-cell immune responses to HER2 produced by active vaccination have been proven using HER2-specific vaccines [3]. The development of novel bioinformatics methods for neoantigen prediction has shown

promising outcomes. This might spur more research on tailored, neoantigen-based cancer vaccines, particularly those for breast cancer [2].

3. Hormone receptor positive breast cancer

Hormone receptor-positive (HR+) breast tumors account for around 70–80% of cases, and they are categorized as either luminal A or luminal B molecularly. The endoplasmic reticulum's ability to bind to estrogenic ligands, such as 17β-estradiol, in order to control and activate its canonical signaling pathways, makes it a valuable biomarker [4]. Expression of endoplasmic reticulum is thought to be a predictive and prognostic sign for breast cancer, as well as a hallmark of hormone-dependent breast tumor development. The first targeted medication authorized for the treatment of hormone receptor-positive breast cancer (HR+ BC) was anti-estrogen therapy. Other additional targeted medicines have since been discovered as a result of a fuller knowledge of the biology and underlying processes of hormone receptor-positive breast cancer [5]. Systemic treatment is becoming more popular for treating hormone receptor-positive (HR+) breast cancer. PI3K inhibitors, mTOR, and CDK4/6 inhibitors are among the targeted medications that are currently licensed for use in conjunction with endocrine therapy. Nowadays, endocrine treatments include aromatase inhibitors (AIs) and selective endoplasmic reticulum modulators (SERMs), continue to be the mainstay of treatment for primary HR+ breast cancers. In addition, in premenopausal women undergoing chemotherapy, ovarian suppression combined with adjuvant endocrine therapy improves survival. Adjuvant endocrine therapy has changed the natural course of HR+ breast cancer, and sometimes the biology of a breast cancer recurrence differs from that of the initial tumor [4].

A family of medications known as SERMs competes with estrogen for binding to the endoplasmic reticulum and then acts on target tissues in an anti-estrogenic or estrogenic manner. Tamoxifen functions similarly to estrogen in other tissues, such as the bone, uterus, liver, and clotting proteins, however it blocks the activity of natural estrogens in normal breast and breast cancer cells. Tamoxifen's anti-estrogenic action lowers the risk of both in situ and invasive breast cancer. When using prolonged tamoxifen for five to fourteen years, the cumulative risk of recurrence was 21.4%, and the death rate from breast cancer was 12.2% when taking extended tamoxifen as opposed to 15.0% when taking it alone. Tamoxifen is beneficial for women with early-stage and advanced breast cancer, regardless of menopause. According to available data, tamoxifen appears to exert its carcinogenic effects on epithelial cells via estrogenic and non-genomic routes rather than directly causing genomic alterations in endometrial cells [5].

The mechanism of action of aromatase inhibitors (AIs), a relatively new class of medications for postmenopausal women with hormone-sensitive breast cancer, is the suppression of aromatase. Because this enzyme changes androgens into estrogens, the inhibitory impact of AIs may exacerbate the estrogen deficiency linked to spontaneous menopause, either alone or in conjunction with agonists that release the hormone luteinizing hormone (LHRH) [5]. In this context, the introduction of AIs has had a significant impact on the treatment of breast cancer, considering their ability to prolong patient survival and reduce tumor recurrence [6]. There are now three AIs on the market: exemestane is a steroidal AI, while anastrozole and letrozole are two nonsteroidal AIs. Comparisons of tamoxifen, tamoxifen with AIs in sequence, combinations of tamoxifen and AIs, studies evaluating the effectiveness of or other AIs in adjuvant treatment for postmenopausal women with early-stage breast cancer [5].

Palbociclib, ribociclib, and abemaciclib are the three oral CDK 4/6 inhibitors that are now licensed for the treatment of hormone receptor-positive metastatic breast cancer (HR+mBC). The enzymes CDK4 and CDK6 are in charge of phosphorylating retinoblastoma proteins so that they become ineffectual [5]. Tumorigenesis is promoted by direct and indirect (via stimulation of CDK2) phosphorylation of Rb to facilitate G1/S transformation. The majority of patient malignancies still include wild-type Rb, and the G1 cell cycle is prevented in these cells by inhibiting overexpressed or overactivated CDK4/6. CDK4/6 inhibitors function by decreasing cell entrance into mitosis or

causing apoptosis in a way that is independent of Rb, even in Rb(-) cancers [7]. Since retinoblastoma proteins are often undamaged in breast cancer, CDK4/6 inhibition is a promising treatment approach.Leukopenia (less prevalent in abemaciclib), lethargy, nausea, diarrhea (more common in abemaciclib), hepatic dysfunction, and anemia are side effects linked to CDK4/6 inhibitors [5]. While CDK4/6 may not be necessary for normal cells, it is necessary for the proliferation of malignant cells. As a result, killing the adversary without endangering the allies is safe. When combined, these characteristics make CDK4/6 a desirable and secure target for anti-cancer treatment [7]. For the majority of patients with HR + mBC, combination therapy with an AI and a CDK 4/6 inhibitor is the recommended initial course of treatment [5].

At present, with the vigorous development of precision medicine, single endocrine therapy has been difficult to bring more effective survival benefits to patients with ER + breast cancer. In order to maximize the use of drug therapy and shrink tumors, a large number of clinical trials have explored a variety of clinical drug regimens.

4. BRCA Mutation-associated Breast Cancer

Mutations that lead to functional inactivation of BRCA1 and BRCA2 have been identified in no less than 5% of cases of widespread breast cancer (BC). These genes are breast cancer susceptibility genes responsible for encoding key proteins that maintain DNA homologous recombination repair (HRR). Chromosome 17's long arm contains BRCA1, while chromosome 13's long arm contains BRCA2.Autosomal dominant inheritance characterizes the inheritance of mutations in BRCA1 and BRCA2 [8]. It is possible to inherit variations of BRCA1 or BRCA2 from either parent [9]. They participate in homologous repair of double-stranded DNA breaks by implicitly acting as tumor suppressor genes [8]. They are involved in controlling cell growth as part of tumor suppressor genes. When a mutation occurs in any of these genes, it can lead to uncontrolled cell growth. Therefore, it is crucial to identify individuals who carry variants in the BRCA gene to help implement more regular surveillance and preventive measures to reduce the risk of developing cancer [9]. Large-scale structural changes in genes such as recombination and loss can disrupt the normal functioning of genes, thereby increasing the risk of breast and ovarian cancer [8]. Management encompasses risk reduction through lifestyle changes, treatment, and the performance of surgical procedures such as bilateral mastectomy and/or salpingo-oophorectomy [9].

One essential molecule in the repair of single strand DNA damage is poly ADP-ribose polymerase (PARP), which also has a significant function in the repair of single strain break (SB) DNA damage. In the absence of HR repair activity, PARP inhibitors can cause cancer cells to die synthetically by blocking PARP's function. Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved olaparib and talazoparib for use as monotherapies. Both medications function by preventing PARPase from acting, which is a crucial component of the base excision repair process. PARP1 facilitates the transfer of the ADP-ribose portion to the target protein by attaching to the DNA damage and allowing nicotinamide adenine dinucleotide (NAD) to bind to its active site, a process known as PARylation, which is a key step in the recruitment of single-stranded DNA repair effector factors is a key step in the recruitment of single-stranded DNA repair effectors [10]. PARP inhibitors work by creating "traps" at single-stranded DNA breaks, which might cause further double-stranded DNA breaks when DNA replication is being attempted. Double-stranded DNA breaks are usually repaired by homologous recombination repair (HRR) mechanisms [11]. When PARP1 auto-PARs, it dissociates from DNA and reverts to a catalytically inactive state. HRR gene mutations are present in tumor cells, and PARP inhibitor therapy utilizes a mechanism known as synthetic lethality. These inhibitors bind to PARP and prevent its PARylation, thereby immobilizing the inactivated PARP on DNA. This action interferes with the DNA replication process, ultimately leading to the creation of DNA double-strand breaks [10]. By restricting PARP to specific DNA damage sites, HR-deficient cells can be effectively eliminated [12]. PARP enzymes are involved in a variety of cellular functions, including gene transcription, apoptosis, and immune

responses. Thus, PARP inhibitors may exert efficacy through multiple mechanisms. The use of PARP inhibitor therapies in patients with early-stage breast cancer and without gBRCA mutations requires validation of their efficacy through clinical trials, which have not yet been approved by regulatory agencies such as the FDA and EMA. As the need for actionable mutation detection increases, the use of BRCA-specific and multigene panel tests will need to become more widespread and predictive models will need to be validated to determine the probability of mutation [10].

One of the best strategies for lowering the risk of breast cancer in women with BRCA mutations who have not yet acquired breast cancer is prophylactic bilateral mastectomy, or RRM. Depending on their age, women who undergo RRM can receive varying degrees of expected benefit. For example, women who undergo RRM at age 25 may have an 8.7 percent increased probability of survival at age 80, while the increase at age 50 may be only 2.8 percent. Women with BRCA mutations may make different decisions than women without the gene depending on whether they have cancer or not; 61% of cancer patients choose to have bilateral RRM. Before genetic testing, the patient should receive enough information and counseling because learning that they have a BRCA mutation is a big choice. Women who have been examined, even if the test results reveal a BRCA mutation, do not regret taking this option, despite the possibility that genetic testing might result in some psychological issues [8].

5. Conclusion

A thorough analysis of targeted treatments for various molecular subtypes of breast cancer is given in this review article. The article highlights treatment approaches for triple-negative breast cancer (TNBC), human epidermal growth factor receptor 2-positive (HER2+), and hormone receptor-positive breast cancer (HR+) and goes into great depth on the relevant targeted medicines and processes. The article points out the importance of individualized treatment regimens for breast cancer, emphasizing the growing importance of biomarkers in guiding therapeutic decisions. In addition, the article explores the mechanisms of resistance to targeted therapies and the potential for new drugs and combination therapies. By discussing the effect of BRCA gene mutations on breast cancer risk and the usage of PARP inhibitors in these patients, the paper contributes to a deeper knowledge of breast cancer treatment. When read as a whole, this article offers a thorough review of targeted treatments for breast cancer as well as a valuable reference and prognosis for upcoming studies and clinical applications. However, primary or secondary resistance to targeted therapies remains a troubling problem, and innovations in new drug development and clinical trial design are urgently needed. In the future, people also look forward to more drugs and their evidence-based evidence to provide more treatment options and more cure possibilities for breast cancer patients.

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