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A Comprehensive Overview on Targeted Therapy for Breast Cancer

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ABSTRACT

With the advent of targeted drugs that aim to disrupt particular pathways that promote tumour growth and survival, the therapeutic choices for breast cancer have expanded dramatically during the last 25 years. The tremendous advancements in our knowledge of the biology of breast cancer make these discoveries possible. Despite their long-standing promise, a thorough evaluation of the efficacy and impact of targeted therapies has been made feasible by the accumulation of clinical experience with a variety of medications and therapy classes. The successful targeted therapies for breast cancer that are presently being employed in clinical settings will be the main topic of this study. They will be discussed together with their indications, clinical data summary for the various subtypes of breast cancer, and impacts on disease progression, survival, and related side effects. The success of certain therapy classes and how it impacts patient outcomes will receive special focus. A review of potential future research avenues and an analysis of the function of targeted drugs in the management of breast cancer will round out the study.

INTRODUCTION

Breast cancer necessitates unique therapeutic management strategies because it is a complicated disease with a range of clinical symptoms, genetic alterations that contribute to its progression, and varying responses to treatment.It remains the second most frequent cancer in women and a major cause of mortality globally. As our knowledge of the biology of cancer has grown, targeted medicines that target the molecular pathways linked to carcinogenesis have been created.Treatment options include hormone therapy, chemotherapy, targeted HER2 medicines, surgery, and radiation, with the most common subtypes identified by HER2 expression, oestrogen receptor (ER), and progesterone receptor (PR). These markers are absent in triple-negative breast cancer (TNBC), the aggressive type of the disease that affects more young and premenopausal women and has fewer treatment choices. New targeted medicines have been created as our knowledge of the biological mechanisms and molecular changes causing cancer has grown.Unexpectedly, obesity is associated with hyperestrogenism and a higher risk of breast cancer, which frequently occurs after menopause. On the other hand, being overweight is linked to anovulatory periods in premenopausal women, which are linked to a lower risk of cancer. While not all epidemiological research have confirmed the negative effects of hormone replacement therapy and oral contraceptives, some have.

TARGETED THERAPY FOR BREAST CANCER

HER2-Targeting Antibodies

The development of medications that target HER2, often referred to as ERBB2, represents a significant breakthrough in targeted therapy for breast cancer. HER2 is a transmembrane tyrosine kinase receptor that affects angiogenesis, invasion, metastasis, differentiation, and cell proliferation. Tyrosine phosphorylation occurs when HER2 and Epidermal Growth Factor Receptor (EGFR/HER1) heterodimerise, initiating a mitogenic response.In the groundbreaking study by Slamon et al., five HER2 gene amplifications and breast cancer outcomes were first connected.6. They found that HER2 amplification, which is linked to a higher risk of relapse and death, is present in 53 out of 189 (28%) original human breast tumours.These findings provided a strong foundation for developing HER2-targeting therapies.7.The first such drug approved for clinical usage was trastuzumab, a humanised monoclonal antibody that binds to an extracellular epitope on HER2. Trastuzumab binding causes receptor downregulation in HER2-overexpressing cancer cells, effectively preventing proliferation and promoting death.8.

TK- Tyrosine kinase inhibitors

Since HER2 has been identified as a key oncogenic driver in breast cancer, oral small-molecule inhibitors that target its catalytic activity have been produced. Lapatinib, the first tyrosine kinase inhibitor approved for the treatment of breast cancer, competitively inhibits both EGFR and HER2. It may selectively induce apoptosis and growth arrest in breast cancer cell lines that overexpress HER 2.9, according to preclinical study.In the EGF100151 phase III clinical trial, lapatinib plus the chemotherapeutic medication capecitabine were evaluated as a second-line treatment for advanced HER2+ breast cancer. The HER2+ clinical stage IIIb-IV breast cancer of the participants had progressed despite prior treatment with trastuzumab, taxanes, or anthracyclines. Patients were randomly assigned to receive either capecitabine alone or in combination with lapatinib.10. These results led the FDA to quickly approve lapatinib and letrozole as treatments for HR+/HER2+ metastatic breast cancer.

HER2-Targeted Antibody-Drug Conjugates

When trastuzumab was created in the late 1990s, it significantly improved overall and progression-free survival while maintaining the quality of life for patients with HER2+ breast cancer. Previous studies have demonstrated that transtuzumab can cooperate with antimetabolites such vinorelbine or docetaxel. Vinca alkaloids are not nearly as good in binding β-tubulin and preventing microtubule assembly as maytansinoid derivatives like DM1. However, systemic administration of DM1 is not feasible due to its extreme toxicity.11.Because trastuzumab emtansine exclusively delivers DM1 to HER2+ tumour cells, it was created to reduce systemic adverse effects. This ADC preserves the HER2-binding affinity of trastuzumab by binding DM1 via a nonreducible thioester linker. Targeted cytotoxicity is made possible by the intracellular release of DM1 via proteolytic digestion and the endocytosis of the antibody-receptor complex following HER2 activation. Additionally, trastuzumab emtansine triggers the antitumor immune response, which may further increase the efficacy of treatment. The efficacy of trastuzumab emtansine, demonstrated in both trastuzumab-sensitive and trastuzumab-resistant preclinical models, suggests its potential use in patients with relapsed or refractory illness following prior trastuzumab therapy.Twelve

Targeted Therapies for HR+/HER2- Breast Cancer

- **CDK4/6 Inhibitors**

CDK4/6 inhibitors, such as palbociclib, ribociclib, and abemaciclib, have fundamentally altered the treatment of HR+/HER2- breast cancer. These medications target them because they are crucial for encouraging cell cycle progression from the G1 to the S phase. By inhibiting this pathway, CDK4/6 inhibitors restore cell cycle regulation, leading to cell cycle arrest and accelerated mortality of cancer cells. Palbociclib (PD 0332991) is a potent and selective inhibitor of CDK4 (IC50 = 11 nM) and CDK6 (IC50 = 16 nM). Similar to abemaciclib, palbociclib has demonstrated efficacy against ER-positive (ER+) breast cancer cell lines. Remarkably, it has been shown to restore sensitivity in tamoxifen-resistant cancer cells, which is in line with evidence that tamoxifen resistance is mediated by CDK4/6. combination.13.When trastuzumab was created in the late 1990s, it significantly improved overall and progression-free survival while maintaining the quality of life for patients with HER2+ breast cancer. Previous studies have demonstrated that transtuzumab can cooperate with antimetabolites such vinorelbine or docetaxel. Vinca alkaloids are not nearly as good in binding β-tubulin and preventing microtubule assembly as maytansinoid derivatives like DM1. However, systemic administration of DM1 is not feasible due to its extreme toxicity.11.Because trastuzumab emtansine exclusively delivers DM1 to HER2+ tumour cells, it was created to reduce systemic adverse effects. This ADC preserves the HER2-binding affinity of trastuzumab by binding DM1 via a nonreducible thioester linker. Targeted cytotoxicity is made possible by the intracellular release of DM1 via proteolytic digestion and the endocytosis of the antibody-receptor complex following HER2 activation.

- **mTOR Inhibitors**

The mechanistic target of rapamycin (mTOR) is an essential component of the PI3K/AKT/mTOR signalling pathway, which regulates cell growth, proliferation, and survival. The deregulation of this system is one of the primary reasons of endocrine resistance in HR+/HER2- breast cancer. One of the mTOR inhibitors developed to target this system and improve treatment outcomes in resistant cases is everolimus. Everolimus, an oral mTOR inhibitor, has demonstrated significant efficacy when combined with endocrine treatment. Patients were given either everolimus or a placebo in addition to trastuzumab and paclitaxel. In the intention-to-treat group, everolimus had no effect on the objective response rate, clinical benefit rate, median progression-free survival, or overall survival.Everolimus plus exemestane significantly increased progression-free survival (PFS) compared to exemestane alone in patients with advanced HR+/HER2-breast cancer who had progressed on previous nonsteroidal aromatase inhibitors in the key BOLERO-2 investigation. Thus, everolimus was found to be a beneficial treatment option for patients with endocrine-resistant illnesses. Despite its effectiveness, everolimus has side effects that should be avoided, including stomatitis, exhaustion, and hyperglycemia. Dosage adjustments or supportive care may be necessary for treatment adherence. Ongoing research is looking into mTOR inhibitor combos with other targeted medications, including as CDK4/6 inhibitors and PI3K inhibitors, to circumvent resistance mechanisms and enhance therapy efficacy. These strategies aim to expand the benefits of mTOR inhibition to bigger patient groups and enhance treatment customisation.14

PI3K Inhibitors

Mutations in the PIK3CA gene, which codes for the catalytic subunit of PI3K and is present in around 40% of HR+/HER2- breast tumours, are associated with a poor response to endocrine therapy. To aid patients with endocrine-resistant disorders, PI3K drugs have been developed that target this pathway. Alpelisib is a PI3Kα selective oral inhibitor designed for patients with PIK3CA-mutant HR+/HER2-breast cancer.

In contrast to fulvestrant alone, alpelisib + fulvestrant significantly improved progression-free survival (PFS) in patients with advanced disease and a PIK3CA mutation in the SOLAR-1 study. As a result, the FDA approved alpelisib for this specific patient category. Alpelisib's most common side effects include rash, diarrhoea, and hyperglycemia. Hyperglycemia, a side effect of PI3K inhibitors, should be constantly watched and treated in patients who already have diabetes or impaired glucose tolerance.15.

Targeted Therapies for Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC), a varied and aggressive subtype, is characterised by the lack of expression of the progesterone receptor, oestrogen receptor, and HER2. It accounts for around 10-15% of all breast cancers and is associated with poor overall survival and high recurrence rates due to the lack of alternatives for targeted treatment. However, recent advancements have resulted in several customised therapies, providing TNBC patients with new hope.16

TROP2 Antibody-Drug Conjugates

TROP2 is a cell surface protein that is overexpressed in breast cancer and other malignancies, making it a viable therapeutic target. TROP2 stimulates tumour growth and metastasis by its function in cell adhesion, motility, and signalling. TROP2's high expression on tumour cells, especially in triple-negative and HR+/HER2-breast cancers, has made it a potential target for antibody-drug conjugates (ADCs), which combine the destructive potency of chemotherapy with the specificity of monoclonal antibodies. One of the most researched TROP2-targeted ADCs is sacituzumab govitecan. It is made up of an anti-TROP2 monoclonal antibody and SN-38, the active metabolite of the chemotherapy drug irinotecan. When the antibody component binds to TROP2 on tumour cells, the ADC is internalised.Once within the cell, SN-38 prevents topoisomerase I from damaging DNA, which ultimately results in cell death. In clinical trials for HR+/HER2- breast cancer and metastatic triple-negative breast cancer (TNBC), sacituzumab govitecan has shown promising results, notably improving overall survival and progression-free survival. Because of its exceptional effectiveness in treating patients with metastatic, heavily pretreated TNBC, the FDA granted it quick approval. Sacituzumab govitecan is being developed with ADCs that target TROP2. These treatments combine a range of cytotoxic drugs with anti-TROP2 antibodies to improve targeting accuracy and decrease off-target effects. Even while some of these ADCs have shown encouraging results in preclinical models and early-phase clinical studies, research to determine their potential for treating various cancer types, including breast cancer, is still ongoing.17

Immune Checkpoint Inhibitors

Immunocheckpoint inhibitors are a class of immunotherapies designed to boost the body's immune response against cancer by blocking checkpoint proteins that regulate immune activity. Checkpoint proteins, such as PD-1 (programmed cell death protein 1), PD-L1, and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), frequently function to prevent excessive immune responses that may endanger healthy tissues. However, in cancer, these channels are often used by tumour cells to evade immune system identification, allowing them to multiply and spread.By "releasing the brakes" on the immune system, immune checkpoint inhibitors stop these proteins, allowing the immune system to more effectively target and destroy cancer cells. Particularly when combined with other drugs, immunocheckpoint inhibitors have shown promise as a potential treatment option for breast cancer, particularly triple-negative breast cancer (TNBC).18

Targeted Therapies for BRCA1/2-Mutated Breast Cancer

Breast tumours associated with gene mutations (BRCA1 or BRCA2) present unique treatment options and challenges. Tumours with BRCA1/2 mutations are more susceptible to treatments that concentrate on DNA damage repair because of these mutations, which impact DNA repair mechanisms, particularly the homologous recombination repair (HRR) pathway. Targeted medications that exploit this vulnerability are increasingly being used to treat BRCA1/2-mutated breast tumours, which are often more aggressive and have a bad prognosis. DNA damage accumulates when PARP enzymes, which are necessary for repairing single-strand DNA breaks, are inhibited. This is particularly true in cancer cells where BRCA mutations have previously resulted in defects in DNA repair. Olaparib and Talazoparib are two of the most studied PARP inhibitors in breast cancer.19.

CONCLUSION

By giving patients with different subtypes of the disease more effective and individualised treatment options, targeted drugs have radically changed the way that breast cancer is handled. As our knowledge of the molecular causes of breast cancer has grown, several medication classes that target particular biomarkers and pathways have been created.Treatment has significantly improved the survival rate for HER2-positive breast cancer. These include trastuzumab and pertuzumab, as well as antibody-drug conjugates as trastuzumab emtansine. Similarly, in HR+/HER2- breast cancer, PI3K, mTOR, and CDK4/6 inhibitors in conjunction with endocrine therapy have addressed endocrine resistance and enhanced overall and progression-free survival. The prognosis for triple-negative breast cancer has historically been dismal; new therapies include antibody-drug conjugates, PARP inhibitors, and immunocheckpoint inhibitors. The therapy of BRCA1/2-mutated breast cancer has advanced significantly with the introduction of PARP inhibitors, which target deficiencies in DNA repair.Notwithstanding these advancements, problems persist, including toxicity, novel agent accessibility, and resistance to focused therapy. More research is required to develop next-generation medicines, identify predictive biomarkers, and enhance combination strategies.Targeted medicines are revolutionising breast cancer treatment with new opportunities for improved patient outcomes and quality of life. With sustained creativity and collaboration, precision oncology could advance in the future.

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