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# Targeted Therapy for Breast Cancer: A Review

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## Abstract

Breast cancer is the most common type of cancer found in women and today represents a significant challenge to public health. With the latest breakthroughs in molecular biology and immunotherapy, very specific targeted therapies have been tailored to the specific pathophysiology of different types of breast cancers. These recent developments have contributed to a more efficient and specific treatment protocol in breast cancer patients. Endocrine Therapy for breast cancer currently consist of (1) ovarian function suppression (OFS); (2) selective estrogen receptor modulators (SERMs); (3) selective estrogen receptor down-regulators (SERDs); and (4) aromatase inhibitors (AIs), or a combination of two or more drugs (2). EGFR Inhibitors consist of Trastuzumab conjugates, HER2-targeted vaccines, VEGF Inhibitors, Platelet derived growth factor Inhibitors etc.

**Keywords: Endocrine Therapy, Breast Cancer, hormones, Vaccines, Immunity**

## 1. Endocrine Therapy

Estrogen receptors (ERs) are nuclear proteins regulating the expression of specific genes, and approximately 80% of BCs are estrogen receptor (ER)-positive, of which 65% are also progesterone receptor (PR)-positive. Thus, endocrine therapy (ET) should be considered complementary to surgery in the majority of patients, inducing tumor remission and providing consistent clinical benefit (1). ET has represented the standard adjuvant treatment for ER+ tumors since the 1970s, although the advantages of oophorectomy, adrenalectomy, and hypophysectomy in women with advanced BC had already been demonstrated many years before. ET for BC currently consist of (1) ovarian function suppression (OFS); (2) selective estrogen receptor modulators (SERMs); (3) selective estrogen receptor down-regulators (SERDs); and (4) aromatase inhibitors (AIs), or a combination of two or more drugs (2).

**a. Ovarian function suppression**

Ovaries are the main source of estrogen in premenopausal women, estrogen levels can be reduced by eliminating or suppressing ovarian function. Blocking ovarian function is called ovarian ablation (3). Ovarian ablation can be done surgically in an operation to remove the ovaries (called oophorectomy) or by treatment with radiation. This type of ovarian ablation is usually permanent.Alternatively, ovarian function can be suppressed temporarily by treatment with drugs called gonadotropin-releasing hormone agonists, which are also known as luteinizing hormone-releasing hormone (LHRH) agonists(4).By mimicking GnRH, these medicines interfere with signals that stimulate the ovaries to produce estrogen.

Examplesof ovariansuppression drugsare goserelin (Zoladex), leuprolide (Lupron)(5).

**b. Selective estrogen receptor modulators (SERMs)**

They bind to estrogen receptors, preventing estrogen from binding. Examples of SERMs approved by the FDA for treatment of breast cancer are tamoxifen (Nolvadex) and toremifene (Fareston)(6).Because they bind to estrogen receptors, SERMs can potentially not only block estrogen activity (by preventing estrogen from binding to its receptor) but also mimic the effects of estrogen, depending on where they are expressed in the body. For example, tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone(7).

**c. Selective estrogen receptor down-regulators**

Selective estrogen receptor down-regulators have different pharmacologic characteristics, biochemical structure, and molecular activity with respect of SERM, causing down-regulation and degradation of ERs, and inhibiting proliferation of estrogen-dependent BC cells (8). SERDs are pure ER antagonist, blocks ERs activity and accelerate their degradation, thus exhibiting exclusively anti-estrogen effects. Fulvestrant, the only SERD approved by FDA to treat patients with BC, has 100-fold the affinity of TAM for ER, in lack of adverse effect on endometrial ERs.It is useful especially in patients with advancer BC and as second-line therapy in TAM-resistant tumors (9).

**d. Aromatase Inhibitors (AIs)**

Aromatase activity is expressed especially in the ovary (premenopausal women), placenta, brain, bone and adipose tissue (postmenopausal women). AIs block aromatase enzyme activity, safely reducing circulating estrogen levels only in postmenopausal patients. AIs are ineffective in premenopausal women with functionally active ovary in whom they increase gonadotropin secretion, and therefore estrogen production (10). The combination of AIs and ovarian function supressor using a GnRHa to block the pituitary, is usually an effective strategy. According to the conclusions of the STAGE study, 70.4% of postmenopausal patients with early BC treated with an AI (anastrozole) plus GnRHa (goserelin) obtained complete or partial response to therapy, compared with 50.5% of the control group treated with anastrozole plus tamoxifen(TAM) (11).

**2 . EGFR Inhibitors**

**a.Trastuzumab**

Trastuzumab (Herceptin, Genentech Corporation, United States/ Hoffman-Roche, Switzerland), a monoclonal IgG1 class humanized murine antibody, binding the extracellular domain (ECD) of HER2 transmembrane receptor. It was first approved for breast cancer treatment directed against HER2. The mechanism of its antitumor action is by binding to the ECD of the HER2 receptor, including antibody-dependent cellmediated cytotoxicity (ADCC), blockage of ligand-independent HER2 receptor dimerization.(12) Interestingly, the inhibition of downstream signal transduction pathways and angiogenesis, induction of cell-cycle arrest and apoptosisand interference with DNA repair, have also been confirmed as its mechanism in anti-HER2 therapy(13).

**b. Pertuzumab**

Pertuzumab (Perjeta, Genentech, United States/Hoffman-Roche, Switzerland), a humanized recombinant monoclonal antibody, prevents heterodimerization of HER2 with HER3 by interfering with the ligand-dependent HER3 mediated signaling pathway, thus inhibiting the proliferation. This is done by inactivating multiple downstream signaling networks including the phosphoinositide 3-kinase (PI3K/AKT/mTOR) and the mitogen-activated protein kinase (RAS/RAF/MEK/ERK) pathway(14) Complementary to trastuzumab, pertuzumab triggers an ADCC reaction and binds HER2 at a different ECD than trastuzumab. Although pertuzumab monotherapy has only shown modest anti-HER2 efficacy, there may be a synergistic effect when it is combined with trastuzumab(15).

**c. Lapatinib**

Lapatinib (TykerbTM, GlaxoSmithKline, NC, US) is the only intracellular blocker approved for both HER2 and EGFR receptors simultaneously, achieving greater overall inhibitory effects. It acts as a dual reversible TKI for both these receptors, thus blocking the downstream MAPK/Erk1/2 and PI3K/AKT pathways. Lapatinib has been shown to enhance the trastuzumab-dependent cell-mediated cytotoxicity against breast tumor cells, in in vitro studies(16). Lapatinib is metabolized by the cytochrome P450 system, via the 3A4 isozyme, leading to a single metabolite activity against EGFR, without involving HER2. Lapatinib is specially approved for patients with HER2-positive advanced-stage breast cancer showing synergistic activity when combined with anti-HER2 antibodies like trastuzumab. A preclinical study showed that lapatinib inhibited the growth of HER2-positive breast cancer cells that were resistant to trastuzumab and increased the apoptotic effect of anti-HER2 antibodies(17).

**d. Afatinib**

Afatinib, as an oral small molecule, irreversibly inhibits HER1, -2, and -4 receptors. A phase II study in trastuzumab-resistant metastatic patients showed partial response in patients with progressive HER2-positive breast cancer (18). The most frequent AEs related to Afatinib include diarrhea and rash. Another phase II trial has evaluated the efficacy of afatinib, with or without vinorelbine in patients with inflammatory or MBC.LUXbreast 1 is a phase III trial of afatinib or trastuzumab added to vinorelbine in patients with MBC who have received initial chemotherapy plus trastuzumab regimen(19).

**e. Neratinib**

Neratinib is an irreversible pan-HER (HER1, -2, and -4 receptor) and EGFR TKI that inhibits PI3K/Akt and MAPK signaling pathways after HER2 receptor activation. Earlier clinical studies have demonstrated the use of neratinib in HER2-positive patients exposed to prior regimens of trastuzumab or anti-HER2 treatment. Compared with lapatinib, neratinib has been shown to have more valid and consistent inhibitory effect in feasible resistance pathways (20).

**f. Trastuzumab conjugates**

Ado-trastuzumab emtansine (T-DM1) (Kadcyla, Genentech, United States/Hoffman-Roche, Switzerland) is an immunoconjugate of trastuzumab with an effective microtubule inhibitor agent, which is a derivative of fungal toxin emtansine (DM1).This molecule has three capabilities, anti-HER2 function of trastuzumab, DM1 induced cytotoxicity, and tissue specific expression.146 Phase I/II studies have demonstrated good tolerance, considerable ORR, and improved PFS(21). A recent phase I trial confirmed objective responses to trastuzumab-maytansine (T-DM1) antibody conjugate (Genentech Corp., South San Francisco, CA) with the tolerated doses. To date, the KAMILLA study is the largest cohort of patients treated with T-DM1. Consistent with previous randomized studies, T-DM1 has been considered as an effective and tolerable regimen for second-line treatment of HER2-positive metastatic breast cancer patients (22).

**g. HER2-targeted vaccines**

Cancer vaccines and acquired immunity therapy targeting HER2 have been considered as leading strategies for HER2-positive breast cancer treatment. Strategies of cancer vaccines designed to produce specific anti-HER2 immunity are under research, including HER2 peptide-based vaccines, plasmid DNA-based vaccines, and vaccines with HER2 delivering in a viral vector(23). Targeted therapeutic options and future perspectives for HER2-positive. Wang and Xu 5 Signal Transduction and Targeted Therapy Active anti-HER2 immunization could facilitate the ex vivo expansion of HER2-specific T cells in adoptive immunotherapy for the treatment of MBC. Patients immunized with HER2-targeted vaccines could have strong CD8+ cell-specific responses and mediated delayed-type hypersensitivity reactions (24). In prior clinical trials, HER2-specific vaccines have shown efficacy and sustained levels of T-cell HER2 immunity, generating from active immunity. Evidence from prior trials have shown promising results for examining the potential use of HER2 based vaccines, in the adjuvant chemotherapy to prevent the recurrence in high-risk breast cancer patients. In a small group of patients with stage IV breast cancer, a dendritic cell-based vaccine was also been tested. One patient responded a PR, while three demonstrated stable disease (SD) profile for more than 12 months (25). Multiple treatment strategies were applied, including therapeutic alliance of cell-based GM-CSF secreting vaccines and trastuzumab agent. In clinical practice, normal tissues are being challenged with seldom occurrence of severe autoimmunity AEs. Future research would need to focus on developing various types of multi-epitope vaccines (26).

**c. VEGF Inhibitors**

There are three major targets and groups of drugs available for anti-VEGF therapy: drugs interfering with the VEGF ligand, drugs interfering with the VEGFRs and drugs interfering with intracellular signaling of the VEGFRs. Bevacizumab and ramucirumab are monoclonal humanized antibodies designed to inhibit the interaction between VEGF ligands and receptors whereas sorafenib is a tyrosine kinase inhibitor (TKI) targeting VEGFRs, but also with an affinity for other tyrosine kinases, including platelet-derived growth factor receptor (PDGFR) (27).

1. **Bevacizumab** is a monoclonal antibody that binds and inactivates soluble VEGF-A molecules, resulting in inhibition of VEGF-mediated angiogenesis. Bevacizumabwas mainly tested in combination with chemotherapeutic drugs and in the neoadjuvant therapy regimen. These chemotherapeutics include capecitabine, paclitaxel, docetaxel, anthracyclines, gemcitabine and vinorelbine, which are approved chemotherapeutic drugs against breast cancer (28).

2. **Ramucirumab** is a humanized monoclonal antibody against the VEGF-binding domain of the VEGFR-2, which is found to be overexpressed in many human breast cancers and seems be an important receptor facilitating VEGF-mediated angiogenesis. Ramucirumab binds to VEGF-2 with strong affinity and inhibits interaction between tumor-produced VEGF and VEGFR-2. A phase I study from 2010 examined the effect of ramucirumab against different malignant tumors and revealed promising data for ramucirumab in anti-angiogenic therapy (29).

3. **Sorafenib** is a tyrosine kinase inhibitor and exerts an anti-proliferative and anti-angiogenic activity by blocking the intracellular signal transduction of VEGFR-2 in endothelial cells. Monotherapy using sorafenib has not shown significant results in breast cancer. Some trials suggest that due to the fact that sorafenib targets angiogenesis at multiple steps, the agent may be able to affect the pathways involved in the case of bevacizumab-resistance (30).

**d. Platelet derived growth factor Inhibitors**

Drugs like imatinib, nilotinib, and sunitinib are capable of disrupting PDGFR signaling Imatinib. Imatinib mesylate is an anti-cancer targeted therapeutic agent, which can target and suppress receptor tyrosine kinases especially PDGFR-β and c-Kit pathways in breast cancer cell lines by influencing their expression down regulation (31).

**e. Insulin Like Growth factors inhibitors**

IMC-A12, a fully human monoclonal IgG1 antibody binds with high affinity to the IGF-IR and prevents liganddependent receptor activation and downstream signaling. IMC-A12 also mediates internalization and degradation of the IGF-IR. In preclinical animal studies IMC-A12 was found to inhibit growth of a variety of tumors, including breast, lung, colon, and pancreas. Currently, a clinical trial is testing IMC-A12 with antiestrogen such as tamoxifen, anastrozole, letrozole, exemestane or fulvestrant to treat breast cancer (32).

Nordihydroguaiaretic acid (NDGA) is a phenolic compound that inhibits two receptor tyrosine kinases, namely, IGF-1R and HER2. In vitro studies suggested that NDGA induced DNA fragmentation, cleavage of -PARP and caspase-3. Combination treatment of NDGA and trastuzumab resulted in greater efficacy in trastuzumab-refractory cells than either agent alone, suggesting that NDGA increases the sensitivity of refractory cells to trastuzumab. Derivatives of NDGA are currently in clinical trial for several solid tumors (33).

**5. Fibroblast Growth Factor Inhibitors (FGFRI)**

There is a growing interest in FGFR/FGF inhibitors to block the formation and progression of Breast cancer in developing new targeted therapies against this pathway. Clinical evaluations have been conducted over small FGFR inhibitors, selective or nonselective, even though manyare early clinical trials. Lucitanib and infigratinib are most commonly used drugs as FGFRI (34).Lucatinib:- Lucitanib is a newer oral FGFR1-2 inhibitor, although preclinical proteomics analyses suggest it may exert its antitumor activity through additional unidentified targets. Lucitanib assessment in the clinical setting is still at a very preliminary stage. It has been tested in a single phase-I/IIa trial on solid tumors, showing promising results in terms of effectiveness (complete + partial response 26–50% depending on tumor subgroup) with a maximum tolerated dose of 15 mg/day. Cardiovascular toxicity was frequently enountered including hypertension (35).

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