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Immunotherapy Targeting HER2-positive Breast Cancer

Chingman Tan *

School of Biological Sciences and Engineering, South China University of Technology, Guangzhou, 510000, China

* Corresponding Author Email: 202235560018mail.scut.edu.cn

Abstract. Breast cancer with HER2-positive status is highly invasive and susceptible to recurrence and metastasis, and its targeted immunotherapies mAb (e.g., trastuzumab, pertuzumab), ADCs (e.g., T-DM1, T-DXd), and ICIs have enhance the prognosis; however, their drug-resistance and adverse effects still limit their long-term efficacy. Despite advances in immunotherapy targeting HER2+, the indications for ICIs in HER2-positive breast cancer are unclear, the selection of biomarkers for combination therapy remains controversial. This article systematically summarizes several immunotherapeutic strategies for HER2-positive breast cancer and their research progress, including the mechanism of action,resistance management of mAb, the clinical advantages and toxicity risks of ADC , and the potential and challenges of ICI combination targeted therapy. Trastuzumab plus pertuzumab combination chemotherapy can enhance the survival of early-stage patients, while T-DM1 demonstrates safety advantages in drug-resistant second-line therapy; ICI combined with targeted therapy has preliminary efficacy in PD-L1-positive patients, and the specific applicability of the population needs to be further screened. This review provides a theoretical basis for optimizing the precision treatment of HER2-positive breast cancer, and in the future, in-depth exploration of drug resistance mechanisms, development of novel ADC, and combination therapy strategies based on the immune microenvironment are needed to break through the bottleneck.

Keywords: HER2-positive breast cancer; immunotherapy; monoclonal antibody; immune checkpoint inhibitor.

1. Introduction

Human epidermal growth factor receptor type 2 (HER2)-positive breast cancer cases account for approximately 25-30% of all breast cancer cases, and it is one of the most aggressive types among the four subtypes of breast cancer, characterized by a high degree of malignancy, poor prognosis of patients, easy recurrence at an early stage, high metastasis, and is related to the overexpression of HER2. Overexpressed HER2 can dimerise with other EGFR family receptors, activating the heterodimeric intracellular tyrosine kinase (TK), which autophosphorylates tyrosine residues in the intracellular region of the heterodimer and activates a cascade of signaling pathways such as PI3K/Akt, MAPK and PLC-γ to regulate cell proliferation, migration and differentiation, leading to tumourigenesis and increasing the risk of metastasis and recurrence. The cascade of signaling pathways, such as PI3K/Akt, MAPK and PLC-γ,regulate cell proliferation, migration and differentiation, leading to tumourigenesis and causing a greater chance of metastasis and recurrence [1].

Three groups of drugs used for treating HER2-positive breast cancer can be grouped based on their pharmacological mechanisms: monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs). While these drugs have brought about an increase or improvement in survival, mortality and quality of prognosis for breast cancer patients, primary and acquired resistance have also emerged. This has resulted in patients failing chemotherapy and relapsing after treatment.

In fact, immunotherapy is contributing to the enrichment and expansion of treatment options for HER2-positive breast cancer. This article will review and discuss various immunotherapeutic agents

for HER2-positive breast cancer, briefly explain the advantages and disadvantages of these agents, and discuss their application prospects and precautions.

2. Pathogenesis of HER2+

The epidermal growth factor receptor (EGFR) family includes HER2, HER3, and HER4, and HER2 is a member of them, all of which are tyrosine kinases consisting of glycosylated extracellular domains, hydrophobic transmembrane segments, and intracellular tyrosine kinase regions. The EGFR family has the ability to bind to various ligands, including epidermal growth factor and transforming growth factor α. Upon binding to EGFR, EGF activates the appropriate signaling pathways to provide nutrients needed for cell growth. It should be noted, however, that HER2 has not been found to have a ligand to bind to. In addition, Cho found that HER2 exists in an extended and open conformation compared to the bound and closed structures of HER1, HER3, and HER4, and that the exposed dimerization arm of HER2 is not buried but exposed, allowing HER2 to pair with the other three receptors after the other three receptors bind to their respective ligands to form a heterodimer with potent signaling activity [2]. The heterodimer's intracellular tyrosine residues undergo autophosphorylation and activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, which mediates cell survival; the Ras and phospholipase C (PLC-γ) signaling pathways, which are involved in cell proliferation; and the ERK1/2 signaling pathway, which promotes cell division by activating protein kinases and transcription factors, among others. All of these activated pathways regulate the growth, migration and differentiation of breast cancer tumor cells [1].

3. Immunotherapy regarding HER2

3.1. Humanized monoclonal antibody (mAb) for HER2 single target

MAb therapy belongs to molecular targeted therapy, which is an early immunotherapy used to treat this type of cancer, humanized mAb with single target of HER2 has target specificity and low toxicity, and its representative drugs are trastuzumab and pertuzumab.

3.1.1. Pharmacological Mechanisms of Classical mAb

Trastuzumab is the first humanized mAb against HER2 approved for clinical use and the most widely used, with remarkable success in the treatment of HER2+ breast cancer. Trastuzumab inhibits the proliferation of breast cancer tumor cells through various mechanisms, mainly by specifically binding to the IV region of the extracellularly overexpressed HER2 receptor and inhibiting the formation of homodimers. The main mechanisms of trastuzumab include: (1) activation of ADCC, which induces apoptosis and enhances the activity of NK cells through the binding of Fc structural domains to the surface receptors of NK cells, and the synergistic effect of trastuzumab combined with chemotherapy can be achieved; (2) Inhibiting HER3 phosphorylation and activating PTEN can result in the blocking of the PI3K/AKT signaling pathway, and inhibiting the proliferation of breast cancer cells through various mechanisms. to curb the key pathway of tumor proliferation; (3) Regulating the cell cycle, activating p27KIP1 to cause cancer cells to stagnate in the G0/G1 phase; (4) Specifically targeting the HER2 receptor, inhibiting the shedding of its extracellular domains and promoting the endocytosis and degradation of the receptor-antibody complexes, thereby weakening the HER2-mediated carcinogenesis signaling [3].

Stratriti's research indicates that trastuzumab treatment causes an increase in HER2 ubiquitination and degradation, it causes downregulation of HER2 [4]. Molina's experiments showed that trastuzumab inhibits metalloproteinase activity to prevent shedding of the extracellular structural domains of HER2 [5]. There are also mechanisms that are controversial, such as inhibition of angiogenesis in tumor cells to inhibit tumor growth; inhibition of intracellular signaling in tumor cells and DNA repair in cancer cells [6].

Pertuzumab is the second mAb widely used in HER2+ breast cancer treatment after trastuzumab, it is slightly different from that of trastuzumab: Tumor growth is inhibited by pertuzumab by binding to the region in which the extracellular structural domain II is found in HER2, stopping the process of creating its heterodimer with HER3, and inhibiting downstream pro-cancer signaling pathways. It can also activate immune cell-mediated ADCC effect to kill cancer cells. Combined with trastuzumab, dual HER2 blockade can lead to a significant improvement in progression-free survival for HER2 positive breast cancer patients, this strategy has become a key method for treating neoadjuvant and first-line breast cancer in both metastatic and early-stage cancer when combined with docetaxel. The NEOSPHERE trial demonstrated that dual-targeted treatment with pertuzumab and trastuzumab had a higher 5-year mPFS (85% vs 76%) compared with the control group, with a hazard ratio (HR) = (0.54, 98% CI: 0.92-1.00), and the pCR rate of patients was significantly higher than that of other control groups [7]. According to the TRYPHAENA study, the effectiveness of two chemotherapy regimens using trastuzumab and pertuzumab combined with anthracycline-containing versus anthracycline-free drugs was equivalent, with a similar cardiac safety profile and fewer serious adverse events in patients treated with the anthracycline-free chemotherapy regimen [8]. These trials have confirmed the importance of trastuzumab and pertuzumab in the neoadjuvant treatment of HER2-positive breast cancer.

3.1.2. Adverse Effects of mAbs

One of the more severe negative consequences of monoclonal antibodies is cardiotoxicity. Cardiotoxicity can cause congestive heart failure and left ventricular dysfunction. Data from the ADVANI study showed that 9.6-18.7% of HER2+ breast cancer patients treated with trastuzumab had a ≥15% decrease in LVEF, which was 1.5-2.0 times higher than that of patients not treated with trastuzumab [9]. In the APHINITY trial, where pertuzumab was used as an adjuvant, there were 15 cases (0.6%) of heart failure or a significant decrease in LEVF in the trial group compared with 6 cases (0.2%) in the control group [10]. Although this study later confirmed that using trastuzumab and pertuzumab together decreases the likelihood of recurrence in patients with early-stage breast cancer while also reducing cardiotoxicity. However, cardiotoxicity affects patient follow-up, prognosis, and survival, which is an issue that should not be ignored.

PI3K/Akt, HER4/HER2, ERK1/2 and FAK pathways are protective of the heart and the NRG-1/HER2 signaling pathway improves the mitochondrial function and cardiomyocyte metabolism, increases the inward flow of calcium ions to improve the contractile function of the myocardium, and reduces cardiomyocyte injury and apoptosis. When trastuzumab blocks these signaling pathways, it mediates a decrease in oxidative stress, glucose uptake, and mitochondrial oxidative phosphorylation levels in cardiomyocytes, affecting normal cardiac metabolism and disrupting cardioprotective mechanisms. In addition, trastuzumab inhibits DNA topoisomerase IIB in cardiomyocytes, thereby mediating increased ROS production and DNA damage. Currently, the cardiotoxicity from mAbs can reduce early myocardial injury, treat congestive heart failure, and have a protective effect on cardiomyocytes; angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor inhibitors (ARBs) [11].

3.1.3. MAb Resistance and Management Strategies

Primary and acquired resistance to HER2-targeted mAbs such as trastuzumab restricts their efficacy. The main resistance mechanisms are as follows: (1)When PTEN is absent or defective, related pathways like PI3K/Akt/mTOR are activated aberrantly;(2) blockade of receptor-antibody interactions, e.g., MUC4 protects tumor cells from immune surveillance and promotes tumor metastasis by blocking intercellular and intercellular matrices masking HER2 receptor epitopes; (3) activation of alternative pathways, e.g., IGF- IR stimulates increased levels of HER2 phosphorylation and mediates heterodimerization of HER2, resulting in reduced activity and down-regulated expression of able P27K1P1, thereby increasing the potential for resistance to trastuzumab [12]. (4) Alteration of HER2 structure. Trastuzumab is unable to bind to and pharmacologically act on HER2 truncated by the action of metalloproteinases (ADAM10) or by hydrolysis of proteins expressing

extracellular structural domains in cancer cells [13]. In this regard, the treatment strategies against trastuzumab and other mAb resistance are as follows: (1) Use of relevant signaling pathway inhibitors such as the PI3K inhibitor XL147, tyrosinase inhibitors pyrrolitinib and tucantinib, and the mTOR inhibitors everolimus and sirolimus; (2) the use of multi-targeted synergistic blocking drugs, such as trastuzumab and pertuzumab dual-targeted combined with Paclitaxel mAb, the two mAbs bind to HER2 extracellular domains II and IV respectively, and synergistically interrupt HER2 downstream signaling.

3.2. Antibody-Drug Conjugates

ADCs are couplings of antibodies and small molecule drugs, represented by the drugs enmetrastuzumab (T-DM1), detrastuzumab (T-DXd). which can selectively deliver the connected small molecule drug to HER2-positive cells with the aid of antibody's affinity for HER2, so as to achieve better therapeutic effect by increasing the antitumor activity and decreasing the off-target toxicity. Consequently, It is positioned for use in the treatment of breast cancer patients who have failed prior treatment regimens, such as antibodies and TKIs, or who have metastatic breast cancer. It has also been shown to improve survival in patients with drug-resistant, metastatic, HER2-positive and HER2-poor breast cancer.

3.2.1. Representative Drugs and Method of Action of ADCs

Enmetrastuzumab is the first ADC approved for breast cancer treatment, which carries and releases cytotoxic Metanosine (DM1) through targeted binding of the trastuzumab portion and tumor cells, which can damage the microstructure of tumor cell, and at the same time, retains the inhibitory HER2 receptor effects of trastuzumab, which has a good drug-antibody ratio. T-DM1 binds to the extracellular structural domain of HER2, to form a complex that is internalized into tumor cells, and SLC46A3, a direct transporter protein, releases Lys-MCC-DM1 from lysosomes into the cytoplasm. Lys-MCC-DM1 enters into the tumor cells and releases DM1, which binds to and inhibits the polymerization of β-1 microtubule proteins, while promoting the depolymerization of microtubule protein, which in turn inhibits microtubule formation and exerts anti-tumor effects. In vitro studies demonstrated that it has more cytotoxic effects than trastuzumab [14], and the EMILIA phase III experimental clinical trial demonstrated better efficacy and tolerability than trastuzumab, with a 50% reduction in the relative recurrence rate and risk of death in patients [15], the relative improvement in survival without invasive disease was 11.3%. Currently, T-DM1 is approved for the second-line treatment of advanced HER2-positive breast cancer because there is no significant advantage of (T-DM1) alone as a first-line regimen compared to trastuzumab combined with paclitaxel, but it has a better safety profile, so academics believe that, in the future, T-DM1 may be the preferred first-line treatment for patients with contraindications to treatment with paclitaxel.

3.2.2. Adverse Reactions to ADCs

Common adverse reactions to T-DM1 are thrombocytopenia, neutropenia, elevated liver enzymes, non-cirrhotic portal hypertension. Thrombocytopenia is the most frequent adverse reaction to T-DM1 use in hematology. Jonathan et al. showed that T-DM1 inhibits megakaryocyte differentiation and platelet precursor production by disrupting the microtubule cytoskeleton of megakaryocytes and platelets [16]. Megakaryocytes take up T-DM1 via cytosolic uptake, and T-DM1 is also taken up by platelets, after which the active metabolite of T-DM1 disrupts the microtubular cytoskeleton of zones and cells and platelets, inhibits megakaryocyte differentiation, and disrupts the formation of platelet precursors. If platelet counts fall below grade 3 according to dosing adjustment guidelines, T-DM1 therapy should be stopped until they return to grade 1.However, in grade 4 , T-DM1 therapy should be resumed at a lower dose only after recovery, and patients receiving anticoagulation during T-DM1 therapy should be closely monitored.

Hepatotoxicity is also a common and serious adverse effect when using T-DM1, which is one of the black box warnings for TDM-1 therapy. T-DM1 can cause severe increases in liver enzymes, ALT and AST. Yukinori et al.'s experiments found that T-DM1 caused hepatotoxicity through a HER2-

dependent pathway, and at the same time, caused rupture of the outer membrane of the mitochondria, and TNF triggered mitochondria-dependent apoptosis. The pro-inflammatory cytokine TNF-α could further enhance T-DM1-mediated hepatocellular injury; in addition, they found that T-DM1 started to disrupt the cytoplasmic membrane and calcium flowed into the interior of the stem cells after the specific binding of DM1 to CKAP5 on the surface of the hepatocytes, and that the increase in the concentration of calcium in the cytoplasmic lysate of the hepatocytes led to the disorganization of microtubule network, which led to hepatotoxicity [17].To avoid hepatotoxicity caused by T-DM1, it is important to monitor the liver function during treatment and avoid CYP3A4 because DM1 is metabolized by CYP3A4 [18].

3.2.3. Resistance Management Strategies for ADCs

Primary resistance to T-DM1 is relatively rare, acquired resistance occurs from time to time, and most patients eventually develop resistance to T-DM1, especially those who have not received trastuzumab. The main mechanisms of resistance are: ① Loss of trastuzumab activity: down-regulation of HER2 expression or p95HER2 truncation mutation leads to the absence of antibody binding sites, which affects drug internalization and DM1 release; ② Defective endocytosis and impaired transport of HER2: Activation of the HER2-T-DM2 recycling pathway reduces the endocytosis efficiency of the HER2-T-DM1 complex; aberrant expression of cytoskeletal proteins interferes with intracellular transport of the drug; and insufficient acidification of the lysosomal microenvironment (elevated pH) and down-regulation of expression of lysosomal transporter proteins further inhibit the metabolic activation of DM1. ③ DM1-mediated ADCC is impaired: Lysine-MCC-DM1 efflux is promoted when there is an increase in drug efflux transporter protein expression using DM1.Alternatively, cells may escape DM1-mediated cytotoxicity by decreasing the induction of cell cycle protein B1 or increasing the expression of (PLK1), thus allowing cancer cells to complete mitosis and avoid apoptosis [19].

Intervention strategies proposed to address the above resistance mechanisms focus on the following four aspects: first, enhancing the intracellular accumulation concentration of DM1 by inhibiting the function of drug efflux transporter proteins; second, co-application of PLK1 inhibitors, which synergistically induces mitotic arrest of tumor cells in order to overcome the abnormalities of cyclic regulation; third, adopting the dual targeting therapeutic regimen of trastuzumab and pertuzumab to inhibit proliferation and survival of drug-resistant tumors by blocking HER2/HER3 heterodimer formation and its downstream phosphorylation signaling pathway to inhibit the proliferation and survival of drug-resistant tumors; and fourth, using HSP90 inhibitors to promote the degradation of HER2 proteins, thus restoring the therapeutic sensitivity of ADC analogues to tumors with low expression or truncated variants of HER2.

3.3. ICIs

ICIs are still not approved for treating HER2+ breast cancer, but there are plenty of clinical trials going on to combine anti-HER2 targeted therapies with immune checkpoint therapy. The first-line treatment for breast cancer with HER2+ is still based on trastuzumab and pertuzumab combined with chemotherapy at this point,but most patients develop varying degrees of resistance to this treatment after one year, and in order to ameliorate this resistance, the safety and efficacy of trastuzumab and pertuzumab combined with an ICI are being confirmed.

3.3.1. Mechanism of Action of PD-1/PD-L1 Inhibitors

The binding of programmed death 1 receptor (PD-L1) and its ligand (PD1) expressed on the cell surface within the tumor is a major factor in inhibiting the function of anti-tumor T-cells, which helps cancer cells to escape from immune surveillance and inhibits anti-tumor cytotoxic T-cell responses preventing T-cells from killing the tumor cells. ICI helps T-cells to recognize and attack the tumor cells again through the blocking of the binding of PD-L1 and PD-1, while reducing the activation of T regulatory cell apoptosis and increasing the activity and number of T-cells and NK cells,the binding

between PD-L1 and PD-1 is blocked by these two types of cells, which allows them to re-recognize and attack tumor cells, at the same time reducing the activation of T regulatory cell apoptosis, increasing the activity and number of T cells and NK cells, and restarting the anti-tumor immune response in the organism. Simply put, inhibitors of PD-1/PD-L1 restore anti-tumor immune effects in the body primarily by reducing the effects of substances or environments that have an inhibitory effect on T-cell activity and numbers.

3.3.2. Progress in Key Clinical Trials

The PANACEA study focused on the safety and antitumor efficacy of the combination of pembrolizumab and trastuzumab in patients with HER2 overexpressing advanced breast cancer, and of 45 patients with positive PD-L1 expression, 7 (15%) patients achieved objective remission, 4 (8%) patients reached their optimal level of remission, and 11 (24%) patients achieved disease control, whose mean duration was 11.1 months [20]. However, no objective response was observed in PD-L1-negative patients, suggesting that they did not benefit from such combination therapy. The findings suggest that pembrolizumab in combination with trastuzumab has preliminary antitumor activity in patients who have a disease that has advanced locally.,unresectable, or metastatic HER2+ breast cancer, in addition to those who have already been treated with trastuzumab but have gotten resistant to it. particularly in PD-L1-positive patients, but not in PD-L1-negative patients. In the future, it is possible that treating ICI with HER2 drugs may involve combining with anti-PD-1 or anti-PD-L1 may become an effective treatment option for patients resistant to trastuzumab treatment who are PD-L1 positive and have high levels of tumor-infiltrating lymphocytes.

The KATE2 study found a benefit in median progression-free survival in Patients with PD-L1 positivity received treatment with atezolizumab, trastuzumab, and estamine, but not in the PD-L1-negative patient group treated with the same drugs [21]. objective remission rates were similar in the atezolizumab group and the placebo group, at 45% and 43%. Nonetheless, there was a significant distinction in objective remission rates when patients were divided into PD-L1-positive and PD-L1-negative groups. in the PD-L1-positive group, the objective remission rates were 54% and 33% in the atezolizumab and placebo groups, respectively, and in the PD-L1-negative group, the objective remission rates were 39% and 50% in the atezolizumab and placebo groups, respectively. This also seems to suggest that for patients with metastatic or unresectable locally advanced breast cancer who are also positive for PD-L1 expression in their bodies, ICI in combination with a therapeutic agent targeting HER2, such as trastuzumab, may be of benefit to them.

3.3.3. The Future and Challenges of ICI

With potent anti-tumor activity and a specific mechanism capable of inhibiting PD-L1 and PD-1 binding, ICI is thought to have the potential to resistance to initial treatment options for HER2+ breast cancer. Preliminary but limited data to support this theory were also provided by studies such as KATE2, PANACEA in which the efficacy and safety of ICI were confirmed at the conclusion of these studies, with patients in the ICI group experiencing adverse effects very similar to those seen in patients who had been treated in the past with trastuzumab in combination with pertuzumab [20,21]. However, the combination of ICI and targeted drugs has a more obvious effect on patients with PD-L1, while patients with negative PD-L1 do not show the advantages of this combination in various indicators. In summary, it suggests that the tatients who have PD-L1-positive HER2+ breast cancer may benefit more from using ICI and targeted HER2 drugs as a treatment. The therapeutic use of ICI in combination with targeted HER2 therapeutic drugs may depend on various immune-related biomarkers in the patient's body, including, such as the genotype of PD-L1, the genetic characteristics of T effector cells, and the level of tumor infiltration and lymphocyte counts in patients lymphocyte count levels, and various other immune-related cell subtypes and genetic characteristics. In the future, we can focus on the mechanism of action of ICI on PD-L1-positive patients, in-depth analysis of the anti-tumor immune mechanism of ICI, as well as the differences in the efficacy of ICI-targeted therapeutic agents in patients carrying different immune-related biomarker types, subtypes, and expression levels, to design more precise and personalized targeted therapies or drugs for the patients.

4. Conclusion

This article summarizes some of the immunotherapies for HER2+ breast cancer: mAbs, antibody-drug conjugates, and ICIs. MAbs, represented by trastuzumab, improve patient survival by targeting the extracellular structural domain of HER2 to block oncogenic signals, but resistance and cardiotoxicity limit their long-term use. ADC drugs (e.g., T-DM1) show unique advantages in resistance management through precise delivery of cytotoxic drugs, but their hematologic and hepatic toxicity still need to be carefully managed. ICI-combined with targeted therapy has shown initial efficacy in the PD -L1-positive patient population, but is less effective in PD-L1-negative patients.

This article integrates existing clinical evidence to reveal the potential of combination therapy (e.g., dual-targeted antibodies, ADC in combination with chemotherapy) in overcoming drug resistance and reducing toxicity, and emphasizes the importance of biomarkers (e.g., PD-L1 expression, tumor-infiltrating lymphocytes) for individualized treatment. However, there are still limitations in these studies: (1) the mechanism of drug resistance is still unclear, especially the regulation of HER2 signaling pathway; (2) there is insufficient evidence on the long-term safety and efficacy of ICI combination therapy in PD-L1-negative patients; and (3) Cancer vaccines and CAR-T therapies, as well as other innovative immunotherapies, have been explored for use in treating HER2-positive breast cancers.

Future research could focus on the molecular mechanisms of drug resistance, the development of novel ADCs, and the exploration of strategies to remodel the immune microenvironment (e.g., CAR-T cell therapy or bispecific antibodies). In addition, by combining the properties of various immunotherapies and chemotherapeutic agents, we can try to provide a more personalized treatment for HER2+ breast cancer patients, and realize the transition from “one-size-fits-all” to “individualized” treatment.

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