

Breast Cancer and Human Epidermal Growth Factor Receptor 2: Overexpression and Related Drugs

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Abstract. As a prognostic and predictive biomarker of some illnesses, overexpression of HER-2 is seen in roughly 15–30% of breast cancers (also known as BC), 10–30% of gastric/gastroesophageal cancers, and many other types of cancers. Since the overexpression of HER-2 occurs in many types of cancers, the relationship between HER-2 and the diseases urgently needs to be illustrated and corresponding drugs and treatment schemes need to be developed. Up to now, several HER-2-targeted drugs are in use and have become an important part of standard treatment options, including but not limited to Trastuzumab, Pertuzumab, Margetuximab, Trastuzumab Emtansine (T-DM1), etc. Given the high mortality rate and connection between HER-2 overexpression and BC, many of these drugs are used in the treatment and prognosis of BC. Here in this article, a review of the latest studies about the relationship between BC and HER-2 and a simple introduction of them were made and what is most important is that some related drugs targeting HER-2 together with their development were also listed.

Keywords: HER-2; BC; overexpression; drugs; targeted therapy.

1. Introduction

BC is a major type of malignant tumors in women, occurrence of which is very frequent and its prevalence is rising every year. In American and European nations, 25% to 30% of female malignant tumors are BC. According to the data presented by Coussens in 1985, around 1.3 million people worldwide receive a BC diagnosis each year, and 400,000 of them will pass away from the condition. Further study has found that in China, the rate of BC in cities is the second highest among female malignant tumors [1]. In some big cities, the initial cause of the increase in BC cases, and the incidence of BC in rural areas is the fifth highest [2]. At present, BC has become the biggest problem threatening women's health, which attracts much of attention from scientists from all over the world.

HER-2 refers to human epidermal growth factor receptor 2, which is a transmembrane-like protein. Its intracellular region has tyrosine-protein kinase activity and mainly regulates cell proliferation, transformation, and apoptosis. Approximately 20% to 25% of BCs have been discovered to overexpress the HER-2 protein, which is known as HER-2 positive BC and is associated with a disease that is more severe and has a poorer prognosis [3]. A large number of other solid tumors, such as bladder tumor, gastroesophageal junction (GEJ) tumor, gastric tumor, and GEJ tumor and many other types in previous studies have also been found to contain HER-2 overexpression, amplification, and mutation. HER-2 has thus become one of the most popular targets in the medicine market and many targeted drugs have been developed based on this theory.

Structural studies showed that HER-2 includes three domains: the extracellular ligand binding domain (ECD), the short transmembrane domain, and the intracellular tyrosine kinase domain. Given that all three domains of HER-2 have important roles in the signaling pathway, we can imagine that each domain can be independently targeted to inhibit HER-2 signaling effectively. After dimerization between receptors (homologous or heterologous), the downstream tyrosine kinase signaling cascade is activated, thereby triggering cell proliferation and migration. On the one hand, this mechanism leads to poor prognosis (a hallmark of all cancers due to its impact on cell proliferation, migration, invasion, and survival), and on the other hand, it provides a unique possibility to use the monoclonal antibody trastuzumab for targeted treatment, which targets the extracellular domain of HER-2,

thereby changing the normal tyrosine kinase signal. So since the 1990s, this treatment option has fundamentally changed the natural history of HER-2-overexpressed disease.

Trastuzumab, as the first HER-2 monoclonal antibody drug approved for marketing, has epoch-making significance and ushered in a new era of targeted therapy for BC. More than 1 million patients who are diagnosed with HER-2-overexpressed BC worldwide have benefited from trastuzumab treatment [4]. With the arrival of the targeted therapy era, trastuzumab combined with pertuzumab has better efficacy than trastuzumab in neoadjuvant therapy, adjuvant therapy, and late rescue therapy for HER-2-overexpressed BC patients. It is predicted that the development of targeted drugs represented by trastuzumab will be a new hotspot in future disease treatment undoubtedly.

Here in this article, I detailed some information on BC and HER-2, with their relationship also being elaborated. And I also summarized three different kinds of drugs in terms of their different mechanisms targeting HER-2 and a detailed list of some representative drugs of different types were also made. Although the overexpression of HER-2 occurs only in 20%–30% of women who are diagnosed with BC, its application is limited sometimes. However, the beginning of tumor molecular targeted therapy is undoubtedly of great significance as for tumor treatment, and it also indicates that tumor molecular characteristics may be one of the future research hotspots.

2. BC, HER-2, and related drugs

2.1. Basic information on BC

According to previous research, in breast cancer(BC), mammary duct epithelial cells lose their normal properties and multiply abnormally as a result of multiple internal and external carcinogenic stimuli, exceeding the self-healing threshold and turning malignant. Its typical signs include breast mass, nipple discharge, skin changes, nipple, areola abnormalities, axillary lymph node swelling, etc. Breast lumps, drainage from the nipples, enlargement of the axillary lymph nodes, and other symptoms are frequent in the early stages of the disease. Cancer cells may spread to distant locations in the late stage, and many organ lesions develop, directly endangering the patients' lives.

According to the most recent statistics, 2.26 million new instances of BC were diagnosed worldwide in 2020, surpassing the second-place number of lung cancer cases by 60 000 cases and making up 24.5% of all new cancer cases among women worldwide; 680000 deaths, ranking fifth in the world [5]. One in eight cancer patients with a recent diagnosis is BC. The rate of BC has surpassed that of lung cancer, making it the most prevalent kind of cancer worldwide. BC is becoming more common there every year. Every year, more than 300,000 women receive a BC diagnosis. In recent years, eastern coastal areas and major cities with affluent economies saw a significant increase in the prevalence of BC. This outstanding figures alarm the world and push scientists to develop new coping methods.

BC molecular typing is mostly based on immunohistochemistry-detected ER, PR, and HER-2. Er refers to the expression state of estrogen receptors on the surface of tumor cells, and the progesterone receptor's expression status is referred to as PR. Er, and PR are usually expressed together and collectively referred to as hormone receptors, or HR for short. If HR is overexpressed, this type of BC depends on hormone growth in vivo as expressed, by HER-2, the presence of which indicates that this gene contributes to the inhibition of apoptosis, promotion of proliferation, and significantly increased invasiveness of cancer cells. Therefore, based on the results of the detection of the aforementioned three signs, BC is broadly divided into four groups: luminal type A, HR expression overexpressed, HER-2 negative; luminal type B, HR expression overexpressed, HER-2 overexpressed; HER-2 overexpression type, both ER and PR are negative and HER-2 is overexpressed; and three negative types.

Among all types of BC patients, the proportion of BC with overexpressed HR expression is large. According to the data from NCCN, the proportion of HR-overexpressed BC is about 65% - 70%, and the proportion of HER-2-overexpressed is about 8.5% - 15%. However, BC which is HER-2 overexpressed is more dangerous and more likely to spread to other organs. Now that the survival

rate is so low, a significant market is available for this target. HER-2 has thus become one of the popular targets in medicine market.

2.1.1 HER-2 and occurrence of BC

HER-2 is a protein with tyrosine kinase activity that resembles a transmembrane receptor. The HER-2 gene is located on chromosome 17 and primarily encodes the HER-2 protein. Heterodimers frequently choose the HER-2 protein as their partner because of its higher activity when compared to other heterodimers. Tyrosine kinase activity is primarily induced by receptor dimerization and autophosphorylation of the tyrosine kinase region in the cytoplasm when HER-2 binds to the ligand. PI3K/Akt, MAPK, phosphatidylinositol 3-hydroxykinase (PI3K)/Akt, signal transduction and transcriptional activation (STAT), and phospholipase C (PLC) pathways are the major signal transduction pathways that the HER-2 protein mediates, all of which are based on the cooperation of three domains of it. As a result, the HER-2 protein is crucial for several activities such as angiogenesis, cell differentiation, and proliferation. Although detailed information of these microscopic paths is still unclear and complexed, studies undoubtedly indicate its high expression can accelerate cell division, make its proliferation and differentiation process unbalanced, and finally transform into cancer cells, as a consequence of which BC is thus formed. In addition, studies have found that high expression of HER-2 can increase tumor cell migration rate, in vitro invasion rate, and type IV collagenase activity, all of which are associated with poor diagnoses of it and can interfere with the synthesis of adhesion molecules, thereby promoting tumor invasion, metastasis, and recurrence. Variant forms of HER-2 include overexpression, mutation, and amplification, all of which are pathological indicators associated with many types of tumor. As with BC, HER-2 overexpression was most common, and rates of positivity fell for colon and stomach cancer. So HER-2 targeted drugs are main parts of the treatment option as for it, which will be introduced below in detail. Page Numbers

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2.2. Three types of drugs targeting HER-2

At present, there are many targeted drugs for HER-2 overexpressed adenocarcinoma, which are mainly divided into three categories according to their chemical properties, namely, monoclonal antibody drugs, antibody-drug conjugates, and small molecule drugs. The most classic is trastuzumab, and additionally, there are currently pertuzumab, lapatinib, neratinib, pyrotinib, and so on. These drugs are to be found only effective for HER-2 overexpressed BC, but the specific application to which line, still needs to be determined clearly according to the specific condition, which should be pay much attention to. Here is an overview of three kinds of drugs and a list of some representative drugs [6], and an overlook and understanding of the development of such targeted drugs from the author was also made.

2.2.1 Antibody drugs

Antibody drugs such as trastuzumab and pertuzumab mainly target the extracellular binding region of HER-2. By binding HER-2, they block the heterodimerization of HER-2 and other her receptors, thus slowing down the growth of tumors. By the way, it is major part as for therapy of cancers represented by BC.

Trastuzumab(trade name is Herceptin) is the first biological gene-targeted therapy drug in history, which was approved by FDA in 1998. This anti-HER-2 monoclonal antibody is generated from recombinant DNA, and it usually connects to the extracellular region of HER-2 with high affinity and specificity, thus inhibiting HER-2. The authorized indications at this time include metastatic BC with

HER-2 positivity. 2. When combined with paclitaxel or docetaxel for patients with metastatic BC who have not had chemotherapy. Metastatic BC has received one or more chemotherapy regimens as monotherapy. HER-2 overexpressed early BC1. Single-agent adjuvant therapy after surgery, adjuvant chemotherapy with anthracycline antibiotics, and radiotherapy (if applicable); 2. After chemotherapy with doxorubicin and cyclophosphamide, the combination of this product and paclitaxel or docetaxel was used as adjuvant therapy; 3. Adjuvant therapy in combination with docetaxel and carboplatin; 4. Neoadjuvant therapy combined with chemotherapy, followed by adjuvant therapy, is used for locally advanced (including inflammatory) or BC with tumor diameter > 2cm. Clinical trials have shown that it is effective for HER-2 overexpressed patients. 222 instances of chemotherapy failure in patients with advanced BC were treated at two multicenter centers in Europe and the United States with trastuzumab, 8 cases of complete remission, 26 cases of partial remission, the effective rate was 15 % and the effective rate was 18 % in HER-2 strong overexpressed(+++) patients and only 6 % in weak overexpressed patients(+) respectively [7]. Since its approval in 1998, it has contributed significantly to the treatment of BC. Trastuzumab has been listed and incorporated into medical insurance in China, and it is also widely used in domestic patients, which benefits millions of people suffered from BC.

On June 8, 2012, the U.S. FDA approved pertuzumab (trade name: Perjeta) for the treat of metastatic disease in metastatic BC patients with HER2-overexpressed who have not previously undergone anti-HER2 therapy or chemotherapy. By binding HER2, the heterodimerization of HER2 and other her receptors is blocked, thus slowing down the growth of tumors At present, it has become a full-course medication choice for HER2-overexpressed BC patients. Clinical data revealed that the double target group's median survival duration was 57.1 months., and that of the control group was 40.8 months, which increased by 16.3 months. In the trastuzumab + pertuzumab + docetaxel group, 37 % of patients achieved 8-year time of survival, which was much higher than 23 % compared to trastuzumab group [8].

Margetuximab is a new type of HER-2 targeting monoclonal antibody with an optimized Fc domain for immune enhancement. It has similar HER-2 binding and antiproliferation effects compared to trastuzumab, and its optimized Fc domain can enhance antibody-dependent cytotoxicity. The m-optimized Fc domain increased the affinity for the activated Fc receptor cd16a and decreased the affinity for the inhibitory Fc receptor CD32b. The study confirmed that the low-affinity cd16a-158f allele was associated with the reduced efficacy of targeted therapy. Sophia's phase III clinical trial findings revealed that for individuals with advanced BC that was HER-2 overexpressed and who had previously had chemotherapy, trastuzumab, pertuzumab, and 90% who had received t-dm1 treatment progress, the PFS of Margetuximab combined chemotherapy was significantly longer than that of trastuzumab combined chemotherapy, Margetuximab showed greater superiority (6.9 months vs. 5.1 months, HR = 0.68, P = 0.005)[9] and acceptable safety, being similar to trastuzumab Clinical data revealed that the double target group's median survival duration was 57.1 months .

2.2.2 Antibody-drug conjugates

In recent years, in addition to the traditional endocrine, monoclonal antibody, and a small molecule targeted drugs, a new class of antibody-drug conjugates (ADCs) integrating chemotherapy and targeted drugs has become a new hotspot in the field of anticancer drugs and attracted much attention. One end of ADC is an antibody that can specifically recognize cancer cells, and the other end is connected with cytotoxic chemotherapy drugs. Depending on the antibody, chemotherapy drugs can be accurately delivered to cancer cells to kill or kill cancer cells. Compared with normal chemotherapy, ADC has better efficacy and fewer side effects.

Antibody-drug conjugates (ADCs) Trastuzumab Emtansine (t-dm1), enhertu (FAM trastuzumab deruxtecan nxki, trastuzumab deruxtecan, t-dxd, azd4552, ds-8201) and vedolizumab. The main indications of these targeted drugs are HER-2-overexpressed BC, gastric cancer, and lung cancer, ect. It is through endocytosis into cells to release small cytotoxic molecules such as DM1 to kill tumor cells with little effect on other parts of body.

ADC medication targeting HER2 was created by Roche and ImmunoGen under the trade name Trastuzumab Emtansine (T-DM1). It is also the first antibody-drug conjugate in the world and was

approved by the FDA in 2013 for the treatment of cancer patients with metastatic HER2-overexpressed disease who failed trastuzumab and paclitaxel chemotherapy. It is composed of Roche's trastuzumab and ImmunoGen's cytotoxic agent DM1 through a stable linker to deliver DM1 to HER2-overexpressed BC cells, with the characteristics of 'mass destruction' of HER2-overexpressed tumor cells. The results showed that (1) the incidence of iDFS events (disease-free survival) in the T-DM1 group and the trastuzumab group was 91 (12.2%) and 165 (22.2%), respectively. (2) DFS (disease-free survival) rate: 98 (13.2%) VS 167 (22.5%) [10]. In individuals with remaining lesions, T-DM1 is superior to trastuzumab and can dramatically lower the chance of recurrence.

As a new generation of ADC drugs, ds-8201 has unique properties. In an experiment, after an observation of 20.5 months, 37 patients (20.1%) are still receiving ds-8201. The objective remission rate was 61.4% and the duration of remission was 20.8 months; The progression-free survival was 19.4 months; The overall survival rate at 12 months was 85%; At 18 months, the overall survival rate was 74%, and the current data maturity of overall survival was 35%, and the initial median overall survival reached 24.6 months [11].

More than half of the subjects in this study have received 6 kinds of drug treatments, including targeted drugs and endocrine drugs represented by trastuzumab, and belong to patients with severe and refractory BC. These patients can still obtain an objective remission rate of 61.4% after receiving ds-8201 treatment after almost all drug treatments have been exhausted, which is sufficient to confirm the high sustained effectiveness of ds-8201.

2.2.3 Small molecule tyrosine kinase inhibitors

Small molecule tyrosine kinase inhibitors (TKIs), including afatinib, neratinib, erlotinib, lapatinib, and tucatinib, target the intracellular tyrosine kinase region of HER-2 to block signal transduction by inhibiting phosphorylation.

Afatinib, commodity name: Gilotrif, English name: afatinib. Afatinib works based on permanently inhibiting ErbB family receptors. Afatinib inhibits the whole ErbB receptor family continuously and selectively, in contrast to other targeted medicines (such as erlotinib, which is reversible and primarily targets EGFR (ErbB1)). It is mainly used as the first-line treatment of advanced non-small cell lung cancer (NSCLC), the treatment of HER2-overexpressed advanced BC patients, and the second-line therapy for advanced squamous cell carcinoma of the lung. The phase After trastuzumab treatment failed for HER-2 overexpressed BC patients, a second phase study of afatinib revealed some preliminary activity in the treatment of these patients. However, the afatinib for BC brain metastasis effect is not good according to the current test data[12].

Pyrotinib is the first HER-2 drug developed in China. The Phoebe study included 267 patients with HER-2 overexpressed BC who had previously used trastuzumab, taxane, and/or anthracyclines. In the pyrotinib group, the median progression-free survival was 12.5 months, a significant increase over the the median progression-free survival in the lapatinib group (6.8 months, P0.0001). This outcome directly calls into question lapatinib's effectiveness following trastuzumab therapy failure.

Some studies were divided into the group not receiving lapatinib (Group 3a) and the group receiving lapatinib (Group 3b). According to the recist1.1 evaluation standard, the objective remission rate (CNS ORR) of the central nervous system in group 3A was 49%, and that in group 3B was 33%. In groups 3A and 3B, the halfway overall survival was 13.2 months and 15.3 months, respectively, whereas the halfway progression-free survival was 5.4 months and 3.2 months [13]. In individuals who had not undergone lapatinib therapy or who had, lapatinib demonstrated good effectiveness.

The ASCO expert team identified and reviewed 545 literature studies, and identified 14 of them as the evidence basis for the guideline update recommendations, thus forming the selection and recommendations for systematic drug treatment of ASCO HER-2-overexpressed advanced BC in 2022. First line treatment: trastuzumab ± pertuzumab + Taxus. Second line treatment: t-dxd. Third line treatment: t-dm1 is optional without using t-dm1; Tucatinib + trastuzumab + capecitabine; T-Dxd; Nilatinib + capecitabine; Combination therapy regimen of lapatinib; Trastuzumab combination

therapy; Majituximab + chemotherapy; Pertuzumab; Abecilide + fulvestrant + trastuzumab (HR +); Hormone receptor-overexpressed alternative endocrine therapy.

The emergence of trastuzumab opened a new era of HER-2 targeted therapy. Since then, new monoclonal antibodies targeting HER-2, antibody-drug conjugates, and small molecule drugs and maybe many other types have emerged. The three drugs have their advantages and disadvantages, which is evident. In general, trastuzumab is dominant in adjuvant therapy, neoadjuvant therapy, and metastatic therapy for BC, but attention should be paid to the cardiotoxicity of trastuzumab[14] which is very important in treatment. Therefore, the combination of trastuzumab and small molecule drugs can not only reduce its side effects but also expand the scope of application. At the same time, in recent years, antibody-drug conjugates represented by T-DM1 have emerged continuously, with low adverse reaction rates and high tumor cell killing activity, which has become a new direction for the development of BC treatment drugs.

In any case, all of these drug targets are HER-2, so only for HER-2-overexpressed BC, the scope of application is sometimes limited. But it is believed that more studies on the potential relationship between HER-2 and BC will provide accurate guidance and new insights on the use of these drugs. The discovery of new drug targets will also lead to the emergence of more such targeted drugs available. What's more, since three domains of HER-2 are essential for the role of it, other domains except extracellular domain can also be used as targeted areas, which is less seen in the market. As far as I am concerned, this type of drugs which are based on existed theory but be developed from a different perspective are also an innovation spot in the future. When this type of drugs are developed, their effectiveness, safety, and application scope are to be examined and thus can be compared with old drugs, which is beneficial for better treatment schemes of BC. All in all, new drugs based on new mechanism and new drugs based on old mechanism are all underlying areas as for BC therapy.

3. Conclusion

BC and its high incidence and fatality rate along with its huge harm to public health urgent more related studies to be done and more drugs to be developed. Although the relationship between overexpression of HER-2 and BC has been illustrated and some related drugs have been developed and thus benefit the therapy of some types of cancers, it seems that drug research and clinical treatment breakthroughs in HER-2 have not reached the boundary, and breakthroughs and changes will continue to move forward. At the same time, only a part of BC patients showed HER-2 overexpressed, which also limits the application of such drugs. So as for BC treatment, new mechanisms, targets, and related drug research still have a long way to go. Hoping that more exciting discoveries and excellent drugs will come out in the future.

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