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Progress of targeted therapy for HER-2 positive breast cancer

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Abstract: *Breast cancer is now the most common cancer worldwide, and human Epidermal Growth Factor Receptor-2 (HER-2) positive breast cancer is more malignant, prone to recurrence and metastasis, and has a poor prognosis.However, the advent of trastuzumab monoclonal antibody, a targeted drug, has since improved the prognosis of patients, and a series of anti-HER-2 targeted drugs have since emerged, including pertuzumab monoclonal antibody, inetol monoclonal antibody, tyrosine kinase inhibitors (Neratinib, Lapatinib, Pyrrolitinib, Tucatinib), antibody drug conjugates (T-DM1, DS-8201, SYD985), etc.This paper reviews the progress of targeted therapy for HER-2-positive breast cancer by different mechanisms of action as follows.*

Keywords: *breast cancer; human epidermal growth factor receptor 2; targeted therapy; antibody-drug couples; tyrosine kinase inhibitors*

1. Introduction

Breast cancer has surpassed lung cancer as the most common cancer and the fifth leading cause of cancer death in the world, with 2.3 million new cases in 2020 and the number of cases expected to reach 4.4 million by 2070, while its incidence and mortality rates are rapidly increasing in China, as indicated by statistical results [1]. And studies have shown that HER-2-positive breast cancer accounts for 25-30% of all breast cancer strains, and about 75% of HER-2-positive breast cancers have mutations in the p53 protein, which is one of the factors leading to the high malignancy, early recurrence and metastasis, and poor prognosis of this type of breast cancer [2]. Thus, the treatment of HER-2-positive breast cancer has been a hot topic of research. In recent years, as the molecular mechanisms of breast cancer development and progression have been further investigated, more and more targeted therapeutic agents have emerged, providing more treatment opportunities for HER-2 positive breast cancer patients. This article provides a brief overview of the common clinical classification of targeted agents for HER-2-positive breast cancer.

2. Monoclonal antibody drugs

2.1. Trastuzumab

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that inhibits tumor cell proliferation and prevents tumor angiogenesis primarily through multiple modalities. There are three main modes of action: first, specific action on the extracellular structural domain of HER-2, triggering antibody-dependent cell-mediated cytotoxic effects; second, blocking homodimer formation and inhibiting signal transduction system activation; and third, inhibiting the expression of vascular endothelial growth factor. In 1998, trastuzumab monoclonal antibody was approved by the U.S. Food and Drug Administration (FDA) and became the world's first targeted anti-HER-2 drug, which has since changed the course of treatment for HER-2-positive breast cancer patients and improved the outcome and prognosis of HER-2-positive breast cancer patients. The addition of trastuzumab to postoperative adjuvant therapy for patients with HER-2-positive early-stage breast cancer has long been the standard of care, and the efficacy of trastuzumab in patients with HER-2-positive early-stage breast cancer has been confirmed by the results of several important clinical studies. For example, Sun Tonghui et al. [3] concluded that postoperative adjuvant trastuzumab treatment significantly improved

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the prognosis of stage T1 HER-2-positive breast cancer after a follow-up analysis of 618 patients with HER-2-positive early breast cancer after stage T1 surgery. Hu Linyan et al. [4] showed that the addition of trastuzumab to epirubicin + cyclophosphamide + docetaxel chemotherapy regimen significantly improved the disease control rate, 1-year survival rate, and prolonged progression-free survival (PFS) of patients after radical surgery at 1-year follow-up. It is suggested that trastuzumab treatment for HER-2-positive patients after radical breast cancer treatment can significantly improve the clinical efficacy and enhance the survival rate.In terms of neoadjuvant chemotherapy, Dang Shaohua et al. [5] compared HER-2-positive breast cancer patients treated with neoadjuvant chemotherapy alone and neoadjuvant chemotherapy combined with trastuzumab and found that the latter had significantly higher disease-free survival (DFS) and overall survival (OS) than the former. Trastuzumab in combination with chemotherapy is also the current standard of care in the neoadjuvant treatment of HER-2-positive early-stage breast cancer. An analysis of 229 patients with HER-2-positive stage IV breast cancer by Bingjun Xiong et- al. [6] confirmed that trastuzumab was an independent influence on patients' PFS and OS, suggesting that the application of trastuzumab monoclonal antibody is an effective treatment for HER-2-positive stage IV breast cancer and that there is a survival benefit from continuing trastuzumab therapy even after treatment progression. Therefore, trastuzumab-based anti-HER-2 therapy is necessary and effective in the treatment of HER-2-positive breast cancer patients, whether it is early adjuvant therapy, neoadjuvant therapy or advanced recurrent metastatic breast cancer.

2.2. Pertuzumab

Pertuzumab is a humanized monoclonal antibody class that acts on the extracellular structural domain of HER-2 to block the formation of heterodimers between HER-2 and other HER-2 family members, thereby blocking the receptor-mediated signaling pathway and inhibiting the proliferation of tumor cells.The combination of trastuzumab and pertuzumab can further improve the HER-2 overexpression tumor cells [7]. Pertuzumab was approved for marketing by the FDA in June 2012 and is used in combination with trastuzumab and docetaxel for the first-line treatment of HER-2-positive metastatic breast cancer, a regimen that has significantly improved patient prognosis. In December 2018, National Medical Products Administration approved the import registration application for pertuzumab injection, in combination with trastuzumab and chemotherapy, for the adjuvant treatment of patients with HER2-positive early-stage breast cancer prone to recurrence. In an APHINITY study and subgroup analysis of the Chinese population, dual-targeted therapy with trastuzumab combined with pertuzumab was shown to significantly improve survival in HER-2-positive patients with non-invasive cancer compared to trastuzumab monotargeted regimens, especially in the lymph node-positive subgroup, reducing the risk of recurrence by approximately 35%, making dual-targeted combination therapy more recommended for patients with a high risk of recurrence [8-9]. Shi-Fen Huang et al. [10] showed that patients with HER-2-positive breast cancer treated with dual-targeted combination chemotherapy had higher pathologic complete response (pCR) rates than single-targeted combination chemotherapy in neoadjuvant therapy and were well tolerated. The use of pertuzumab in the first-line treatment of HER-2-positive advanced breast cancer is mainly based on the results of the CLEOPATRA study [11], which confirmed that docetaxel combined with trastuzumab and dual-targeted therapy with pertuzumab significantly improved PFS and OS in HER-2-positive advanced breast cancer compared with docetaxel combined with trastuzumab, with an increase in median OS by 16.3 months and an increase in median PFS by 6.3 months.The results of the study by Kausar Suleman et al. [12] are also consistent with those of the CLEOPATRA trial, confirming the good efficacy of pertuzumab in the first-line treatment of HER-2-positive advanced breast cancer.

2.3. Other types of monoclonal antibodies

Inetetamab is the first independently developed monoclonal antibody drug with stronger cytotoxic effects in China, which was approved for marketing in June 2020 and included in medical insurance for the first time in December of the same year. The results of a study by Bianli et al. [13] showed that Inetetamab combined with vincristine in patients with metastatic HER-2-positive breast cancer who had received one or more prior chemotherapy regimens significantly prolonged median PFS, Objective Response Rate (ORR) and disease control rates compared with vincristine alone.Inito monoclonal antibodies are also included as a first-line treatment option for advanced HER-2-positive breast cancer in the Chinese Anti-Cancer Association Guidelines and Specifications for Breast Cancer Diagnosis and Treatment (hereinafter referred to as the guidelines) [14]. Another drug of current interest is the FDA-approved subcutaneous injection of pertuzumab and trastuzumab in a ready-to-use, fixed-dose

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combination with recombinant human hyaluronidase. The results of a clinical phase III FeDeriCa trial [15] confirmed that this fixed-dose subcutaneous injection demonstrated comparable total pCR compared with conventional intravenous infusion, with consistent efficacy and safety. This easy and quick way of subcutaneous injection is also preferred by patients, not only relieving the pressure on medical resources, but also reducing the risk of patient exposure in hospitals and providing patients and physicians with more treatment options [16].

3. Tyrosine Kinase Inhibitors (TKI)

TKI is a small molecule targeted drug that inhibits the proliferation of cancer cells by inhibiting tyrosine kinase activity of epidermal growth factor receptor and HER-2 and blocking downstream signaling pathways. Because they are usually small molecules and can cross the blood-brain barrier, they are potentially advantageous for the treatment of patients with Central Nervous System (CNS) metastases [17]. Due to its different mechanism of action from monoclonal antibody-based drugs, it may be advantageous for patients who have developed resistance after receiving monoclonal antibody-based drugs. The common TKI drugs currently available are lapatinib, neratinib, pyrrolitinib and tucatinib.

3.1. Lapatinib

Lapatinib is a TKI that reversibly blocks the epidermal growth factor receptor and HER-2, inhibits downstream signaling pathways, and enhances trastuzumab dependent cytotoxic effects. It is mainly used clinically in combination with capecitabine in metastatic breast carcinoma (MBC) or advanced breast cancer with HER-2 overexpression previously treated with anthracycline, paclitaxel, or trastuzumab. Zeng Jiajia et al. [18] concluded that the addition of lapatinib to chemotherapy combined with trastuzumab significantly prolonged the median PFS in HER-2-positive MBC patients after the failure of first-line therapy with controlled adverse effects, and was one of the options after the failure of first-line therapy. Wang Su'e et al. [19] demonstrated that the combination of lapatinib and capecitabine was clinically more effective than capecitabine alone in HER-2-positive breast cancer patients, significantly prolonging survival, improving the time to disease progression and PFS, and reducing the metastasis rate of CNS.However, lapatinib in combination with trastuzumab monoclonal antibody did not show superiority over trastuzumab alone in adjuvant therapy, and it had a higher incidence of adverse effects such as diarrhea and rash. The improvement of pCR rates in patients with lapatinib + trastuzumab was inconsistent in different studies of neoadjuvant chemotherapy [20]. Therefore, lapatinib is not recommended for the first-line treatment of early-stage HER-2-positive breast cancer [14].

3.2. Neratinib

Neratinib, a TKI that irreversibly inhibits HER-1, HER-2 and HER-4, was approved by the FDA in July 2017 for the intensive adjuvant treatment of HER-2-positive early-stage breast cancer and was approved for marketing by National Medical Products Administration in 2020. In the Exte NET phase III clinical study [21], patients with HER-2-positive breast cancer underwent intensive oral neratinib therapy for 1 year after standard treatment with trastuzumab-based antibodies, and the results confirmed that neratinib effectively reduced the risk of recurrence and prolonged invasive cancer-free survival. The pan-Asian subgroup of the NALA Phase III bed study, on the other hand [22], showed that neratinib in combination with capecitabine was associated with prolonged median PFS, median OS, median duration of remission, and a lower overall cumulative incidence of disease intervention for CNS in patients with advanced HER-2-positive breast cancer who had received two or more prior anti-HER-2 regimens compared with lapatinib in combination with capecitabine. Currently, neratinib is a new option for HER-2-positive breast cancer after the failure of multiple lines of treatment in advanced stages, especially for its advantages in preventing CNS disease, which also helps to delay the development of brain metastases [23].

3.3. Pyrrolitinib

Pyrrolitinib, an irreversible TKI-like drug with a mechanism of action similar to neratinib, was approved for marketing in China in 2018.In the PHOEBE phase III clinical study [24], patients with HER-2-positive breast cancer who were previously treated with trastuzumab monoclonal antibody and paclitaxel, pyrrolizidine combined with capecitabine was associated with significantly improved PFS

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and controlled toxicity compared with lapatinib combined with capecitabine. The results of Yang H et al. [25] confirmed that pyrrolizidine in combination with chemotherapy improved the PFS and ORR of patients compared to lapatinib in combination with chemotherapy, and for patients who developed brain metastases, their median PFS was also much higher than lapatinib in combination with chemotherapy (6.5 months vs. 3.5 months). Therefore, pyrrolizidine in combination with capecitabine is the preferred recommendation in the guidelines after failure of trastuzumab therapy [14].

3.4. Tucatinib

Tucatinib, a novel effective and reversible TKI-like agent with high selectivity for HER-2, was approved for marketing by the US FDA in 2020 for the treatment of patients with advanced unresectable or MBC HER-2 in combination with trastuzumab monoclonal antibody and capecitabine, including those who have brain metastases and have received 1 or more previous anti-HER-2 regimens [26]. The HER-2 CLIMB study confirmed that the tucatinib combined with trastuzumab and capecitabine treatment group significantly improved patients' PFS and OS compared with the placebo combined with trastuzumab and capecitabine control group, while their median CNS-PFS and median CNS-OS were also significantly prolonged in patients with established brain metastases [27-28]. In an exploratory analysis, tucatinib improved patients' CNS-ORR by more than twofold compared with placebo, significantly reducing the risk of CNS progression and the risk of death [26]. As tucatinib continues to have a positive impact in clinical trials, it is gradually raising expectations for its application and bringing more treatment options to patients.

4. Antibody-Drug Conjugate (ADC)

ADC is a new type of targeted drug formed by the coupling of a target-acting monoclonal antibody and a cytotoxic chemical, whose mechanism of action is mainly to cause a cytocytic reaction and release cytotoxic effects after lysosomal digestion, thus killing tumor cells [29]. Common antibody-drug conjugates include T-DM1, DS-8201a and SYD985.

4.1. T-DM1

T-DM1 is a combination of trastuzumab and a chemotherapeutic drug, metanephrine, that retains the activity of trastuzumab monoclonal antibody while delivering potent anti-tumor activity to HER-2 overexpressing tumor cells.According to EMILIA, T-DM1 improved PFS and OS over capecitabine combined with lapatinib in patients with HER-2-positive advanced or MBC treated with trastuzumab and paclitaxel, while Ramagopalan SV et al. conducted a real-world study based on the US FH database, and the results further supported T-DM1 therapy as a treatment option for patients with HER-2-positive advanced or MBC [30]. The significant efficacy and good safety of T-DM1 in the treatment of HER-2-positive advanced breast cancer was confirmed by Yan Bingxue et al. [31] after performing Meta-analysis. In Chinese HER-2-positive patients in the KATHERINE trial who had not achieved pCR after previous neoadjuvant therapy with a trastuzumab-containing antibody regimen, adjuvant therapy with T-DM1 significantly improved survival without invasive cancer and had a significantly lower risk of recurrence and death compared with trastuzumab monoclonal antibody [32]. The American Society of Clinical Oncology guidelines also recommend that patients with Her-2-positive breast cancer who do not achieve pCR after standard preoperative chemotherapy and HER-2-targeted therapy should be given 14 cycles of adjuvant T-DM1 therapy [33]. After Meta-analysis, Yan Bingxue et al. [34] concluded that the neoadjuvant regimen containing T-DM1 for the treatment of early HER-2-positive breast cancer showed improved pCR rate and 3-year DFS rate compared with other targeted therapies, but the pCR rate of patients did not show significant advantage when comparing T-DM1 with dual-targeted therapy of trastuzumab combined with pertuzumab, and more clinical studies are needed for further evaluation in the future to bring maximum benefit to patients.

4.2. DS-8201a

DS-8201a, a novel ADC consisting of a trastuzumab , an enzymatic peptide linker, and a novel DNA topoisomerase I inhibitor, delutecan, was approved by the US FDA in December 2019 for the treatment of unresectable or metastatic HER-2-positive breast cancer [35]. Based on the results of the DESTINY-BREAST03 study, the first comparison of DS-8201a with T-DM1 in patients with unresectable or metastatic HER-2-positive breast cancer treated with trastuzumab and paclitaxel

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showed that DS-8201a significantly improved patient PFS (25.1 months vs. 7.2 months), delayed patient disease progression and reduced risk of death by 72%, had a much higher ORR of 79.7% than T-DM1 at 34.2%, also had a significantly better ORR than T-DM1 in patients with brain metastases, and showed a trend toward improved overall survival and a favorable safety profile. These clinical data support that DS-8201a will change the standard of care for HER-2-positive advanced breast cancer [36]. In addition, DS-8201a can also have a killing effect on tumor cells with low HER-2 expression due to its bystander effect.DESTINY-BREAST04 is a phase III clinical trial on this, and if positive results are obtained in clinical trials, DS-8201a may become one of the many clinical staging breast cancer and even triple-negative breast cancer one of the few treatment options available after multiple lines of treatment for advanced metastases [37].

4.3. SYD985

SYD985 consists of a combination of trastuzumab monoclonal antibody and doxorubicin, which can be fractured extracellularly to release cytotoxic drug components into the microenvironment and thus exert anti-tumor effects. A phase III clinical trial, TULIP [38], randomized patients with HER-2-positive advanced or metastatic breast cancer who had received ≥2 prior MBC regimens or had received T-DM1 therapy to the SYD985 and physician's choice groups in a 2:1 ratio and found that the SYD985 group significantly improved patient PFS (6.9 months vs. 4.6 months), but The most frequently reported adverse events in the SYD985 group were conjunctivitis, keratitis and fatigue, so ocular toxicity in patients should be a concern in clinical practice.Based on this study, SYD985 may be a new treatment option for previously treated HER-2-positive breast cancer patients.

In summary, the advent of trastuzumab opened the door to targeted therapy for HER-2-positive breast cancer and has since improved the prognosis of patients. In recent years, in-depth research on a range of targeted agents has given patients at different stages of HER-2-positive breast cancer progression more options to improve their prognosis, but further research is needed on how to choose the sequence of drugs and different combination regimens to achieve individualized treatment for maximum efficacy. More and more efficient anti-HER-2 drugs will be developed and marketed in the future, and we hope that the results of more relevant clinical studies will further promote the development of HER-2-positive breast cancer treatment and bring more hope for the prognosis of HER-2-positive patients.

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