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ARTICLE

Research Progress in Precision Targeted Drug Therapy for HER2-Positive Breast Cancer Patients

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ABSTRACT

HER2-positive breast cancer is an aggressive subtype of breast cancer with poor prognosis. With the continuous development of targeted therapies, the treatment strategies and prognosis for this disease have significantly improved in recent years. This review summarizes the latest advances in the adjuvant and neoadjuvant therapies for early HER2-positive breast cancer, rescue therapies for advanced HER2-positive breast cancer, as well as treatments and prevention strategies for brain metastases in HER2-positive breast cancer. Additionally, the future direction of anti-HER2 targeted therapy is discussed, aiming to provide a reference for clinical treatment.

Breast cancer is one of the most common malignant tumors among women worldwide, with its incidence rising annually. According to the global cancer data released by the International Agency for Research on Cancer (IARC) of the World Health Organization in 2020, breast cancer accounts for 11.7% of all new cancer cases, making it the most common malignancy, and its mortality rate (6.9%) ranks fifth[1]. In China, breast cancer is the second most common cancer among women, with approximately 420,000 new cases and 120,000 deaths each year[2]. Among breast cancer patients, approximately 20% to 30% have HER2-positive breast cancer[3]. HER2 (human epidermal growth factor receptor 2) is a transmembrane protein with tyrosine kinase activity, and its overexpression is closely associated with high invasiveness, recurrence, metastasis risk, and poor prognosis in breast cancer. In recent years, with the in-depth study of the HER2 signaling pathway, various anti-HER2 targeted therapies have emerged,

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greatly altering the treatment landscape of HER2-positive breast cancer and significantly improving patient survival and quality of life. This article provides a review of the adjuvant and neoadjuvant therapy for early HER2-positive breast cancer, rescue therapy for advanced HER2-positive breast cancer, treatment and prevention of brain metastases, and future perspectives.

1. Adjuvant Therapy for Early HER2-Positive Breast Cancer

1.1 Clinical Application of Trastuzumab

Trastuzumab is the first monoclonal antibody approved for the treatment of HER2-positive breast cancer. By binding to the extracellular domain of the HER2 receptor, it inhibits the activation of the HER2 signaling pathway, thereby exerting antitumor effects. Several large clinical trials, such as NSABP B-31, NCCTG N9831, HERA, and BCIRG-006, have confirmed the significant efficacy of trastuzumab in the adjuvant treatment of early HER2-positive breast cancer[4-7]. These studies showed that combining trastuzumab with standard chemotherapy for one year significantly improved patients' disease-free survival (DFS) and overall survival (OS), and reduced the risk of recurrence and death[8]. However, in the NSABP B31 and NCCTG N9831 trials, approximately 5% to 10% of patients experienced a decrease in left ventricular ejection fraction after completing anthracycline-based chemotherapy[9]. The HERA trial confirmed that the standard treatment duration for trastuzumab is 12 months, and about 80% of patients who experienced cardiac events during treatment had reversible symptoms[10]. Therefore, the current standard for adjuvant treatment of early HER2-positive breast cancer is a one-year combination of trastuzumab and chemotherapy.

1.2 Combination Use of Pertuzumab

Pertuzumab is a novel humanized monoclonal antibody targeting HER2. It inhibits HER2 signaling by preventing HER2 from dimerizing with other members of the HER family. The APHINITY trial is a large phase III clinical study evaluating the efficacy of combining pertuzumab with trastuzumab in the adjuvant treatment of early HER2-positive breast cancer. The results showed that adding pertuzumab to chemotherapy and trastuzumab significantly reduced the recurrence rate (11.1% vs. 14.2%) and improved invasive disease-free survival (iDFS) (88.4% vs. 85.8%, HR=0.77, 95% CI: 0.66–0.91), with particularly significant benefits in lymph node-positive patients at high risk of recurrence[11]. This suggests that for early HER2-positive breast cancer patients with high-risk factors, the dual-target therapy of trastuzumab and pertuzumab offers a better prognosis. Additionally, the combination of pertuzumab, trastuzumab, and taxanes has become a first-line treatment for advanced HER2-positive breast cancer, improving overall survival by 16 months[12].

1.3 Sequential Therapy with Small Molecule Tyrosine Kinase Inhibitors (TKIs)

In addition to monoclonal antibody drugs, small molecule TKIs have also been explored in the adjuvant treatment of early HER2-positive breast cancer. Neratinib is an oral TKI that irreversibly binds to the intracellular domains of HER1, HER2, and other HER family members, inhibiting downstream signaling pathways. The ExteNET study evaluated the efficacy and safety of neratinib in HER2-positive early breast cancer patients who had completed one year of trastuzumab-based adjuvant therapy[13]. The results, with a median follow-up of 5.2 years, showed that neratinib significantly reduced the risk of disease recurrence (iDFS: 90.2% vs. 87.7%, HR: 0.73, P=0.0083). Further subgroup analysis revealed that patients with higher recurrence risk factors, such as T2-stage tumors, N2-stage lymph nodes, or prior radiation therapy, benefited more from neratinib, particularly in hormone receptor-positive (HR+) populations (iDFS: 91.2% vs. 86.8%, HR: 0.60, 95% CI: 0.43–0.83). This suggests that sequential use of neratinib after standard trastuzumab-based adjuvant therapy provides an additional therapeutic option for high-risk early HER2-positive breast cancer patients. Moreover, studies also indicate that neratinib shows good efficacy in both early and metastatic breast cancer patients[14].

2. Neoadjuvant Therapy for Early HER2-Positive Breast Cancer

2.1 Application of Trastuzumab in Neoadjuvant Therapy

Neoadjuvant therapy refers to systemic treatment administered before surgery to shrink tumor size, increase the rate of surgical resection, and provide early evaluation of tumor biological behavior. The NOAH study[15] is a key study evaluating the role of trastuzumab in neoadjuvant therapy for HER2-positive locally advanced breast cancer. The results showed that compared to chemotherapy alone, the combination of targeted therapy and chemotherapy significantly increased the pathological complete response (pCR) rate in both breast tissue and axillary lymph nodes, with no significant difference in the incidence of cardiovascular adverse events between the two groups. This indicates that trastuzumab combined with chemotherapy

in neoadjuvant therapy effectively improves the pCR rate, creating favorable conditions for subsequent surgery.

2.2 Dual-Targeted Therapy with Pertuzumab and Trastuzumab

The Neosphere trial further explored the use of the dual-targeted combination of pertuzumab and trastuzumab in neoadjuvant therapy for HER2-positive breast cancer. The results showed that the addition of pertuzumab to trastuzumab and docetaxel significantly improved the pCR rate to 45.8%, and the adverse reactions were generally consistent with the trastuzumab monotherapy group[16]. Subsequent studies also confirmed the efficacy and safety of using the combination of pertuzumab, trastuzumab, and chemotherapy in neoadjuvant therapy[17-19]. These results suggest that the dual-targeted therapy of trastuzumab and pertuzumab significantly improves the pCR rate and prognosis in the neoadjuvant setting without significantly increasing adverse events.

2.3 Exploration of Small Molecule TKIs in Neoadjuvant Therapy

Although small molecule TKIs have not yet become a standard treatment in neoadjuvant therapy, related studies continue to explore their potential. For example, the NSABP B-41 trial found that lapatinib combined with trastuzumab was not superior to trastuzumab monotherapy[20]. However, the PHEDRA study showed that the combination of trastuzumab and neratinib resulted in a higher pCR rate than trastuzumab monotherapy[21]. Additionally, the self-developed irreversible small molecule TKI drug pyrotinib, targeting pan-HER receptors, also demonstrated good efficacy in neoadjuvant therapy. In the PHEDRA study, the combination of pyrotinib, trastuzumab, and docetaxel achieved an overall pCR rate of 41%, significantly higher than the control group's 22%[22]. These studies suggest that small molecule TKIs have potential applications in neoadjuvant therapy, but further clinical research is needed to clarify their efficacy and safety in different patient populations.

3. Rescue Treatment for Advanced HER2-Positive Breast Cancer

3.1 First-Line Treatment

For patients with advanced HER2-positive breast cancer, the goal of first-line treatment is to extend survival, alleviate symptoms, and improve quality of life. For many years, the standard first-line treatment for metastatic HER2-positive breast cancer has been the combination of trastuzumab and taxane-based chemotherapy. Research has shown that the progression-free survival (PFS) of patients treated with the combination of lapatinib and paclitaxel is significantly shorter compared to the trastuzumab-paclitaxel combination, with the incidence of grade 3 or higher diarrhea and rash significantly higher in the lapatinib group[23]. The CLEOPATRA trial, a phase III clinical study evaluating the efficacy of pertuzumab combined with trastuzumab and docetaxel in the first-line treatment of advanced HER2-positive breast cancer, showed that the three-drug regimen significantly prolonged both PFS (18.5 months vs. 12.4 months, HR: 0.62, $P<0.001$) and overall survival (OS) (57.1 months vs. 40.8 months, HR: 0.69, $P<0.001$) when compared with trastuzumab and docetaxel alone[24]. Therefore, the combination of pertuzumab, trastuzumab, and docetaxel has become the standard first-line treatment for advanced HER2-positive breast cancer. Other chemotherapy agents such as vinorelbine, capecitabine, and carboplatin combined with trastuzumab also show significant efficacy. However, special caution should be taken when combining these agents with anthracyclines due to their significant risk of cardiotoxicity[9].

3.2 Second-Line Treatment

Following progression on first-line therapy, second-line treatment options are important for extending survival. For patients progressing after first-line trastuzumab-based therapy, second-line treatment often involves double-targeted HER2 therapies. In the EGF104900 study, the combination of lapatinib and trastuzumab significantly prolonged overall survival (OS) by 5.5 months compared to lapatinib alone[25]. Another study showed that the combination of trastuzumab and pertuzumab as a second-line regimen also demonstrated efficacy, with a clinical benefit rate of 50% and a median progression-free survival (PFS) of 5.5 months[26]. The EMILIA trial, a phase III study evaluating the efficacy of trastuzumab emtansine (T-DM1) as second-line therapy for advanced HER2-positive breast cancer, showed that T-DM1 monotherapy significantly prolonged PFS (9.6 months vs. 6.4 months, HR: 0.65, $P<0.001$) and OS (30.9 months vs. 25.1 months, HR: 0.68, $P<0.001$) compared to lapatinib plus capecitabine[27]. Therefore, T-DM1 has become the standard second-line treatment for advanced HER2-positive breast cancer worldwide. Additionally, the PHENIX study showed that pyrotinib plus capecitabine significantly improved PFS (11.1 months vs. 4.1 months, HR: 0.18, $P<0.001$) and overall response rate (ORR) (68.6% vs. 16%, $P<0.001$) in patients who had failed treatment with taxanes and trastuzumab[28]. These findings provide a new treatment option for second-line therapy in advanced HER2-positive breast cancer.

3.3 Third-Line and Subsequent Treatments

For patients who have undergone multiple lines of treatment for advanced HER2-positive breast cancer, treatment options become more limited. The choice of therapy must consider previous first-line and second-line treatments, as well as the patient's condition. A study on metastatic breast cancer showed that patients receiving tegafur treatment had a higher objective response rate (ORR) and clinical benefit rate than the control group ($P<0.05$ or $P<0.01$). Post-treatment, markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and TPS (tissue polypeptide-specific antigen) levels were lower than before treatment, with the experimental group showing more significant improvements ($P<0.01$). Additionally, patients' immune cells, such as CD3+ and CD4+, were higher than before treatment, with CD8+ levels being lower, and the changes in the experimental group were greater ($P<0.05$ or $P<0.01$). The adverse event rate was also lower in the experimental group compared to the control group (19.51% vs. 42.86%, $P=0.021$)[29]. Tegafur monotherapy showed promising results in third-line treatment for metastatic breast cancer, with higher disease control rates and response rates, as well as improved tolerance, making it a potentially valuable treatment option.

The DESTINY-Breast03 study, a phase III clinical trial comparing trastuzumab deruxtecan (T-DXd) with T-DM1 in patients with advanced HER2-positive breast cancer after failure of second-line therapy, demonstrated that the T-DXd group had significantly better median PFS (not yet reached vs. 6.8 months, HR: 0.28, $P<0.001$), and showed a significant advantage in OS as well. This suggests that T-DXd may become the new standard of care for patients with advanced HER2-positive breast cancer[30]. Additionally, the NALA study found that pyrotinib plus capecitabine significantly prolonged PFS in patients with metastatic HER2-positive breast cancer who had previously received two or more lines of targeted therapy[31]. Another study showed that adding margetuximab to chemotherapy extended PFS compared to trastuzumab in patients with advanced HER2-positive breast cancer[32], offering new options for patients who have failed multiple lines of therapy.

4. Treatment and Prevention of Brain Metastasis in HER2-Positive Breast Cancer

4.1 Treatment of Brain Metastasis

The brain is a common site for metastasis in patients with advanced HER2-positive breast cancer. Approximately 50% of patients with advanced HER2-positive breast cancer will develop brain metastasis[33]. Brain metastasis is often associated with severe clinical symptoms and poor prognosis. Treatment for brain metastasis typically involves surgery, radiation therapy, and systemic treatment. Due to the blood-brain barrier, many chemotherapy drugs and large-molecule monoclonal antibodies are unable to effectively penetrate the brain tissue. This is where small molecule tyrosine kinase inhibitors (TKIs) have an advantage. For example, a multicenter, single-arm, double cohort phase II study evaluating the efficacy and safety of pyrotinib combined with capecitabine in patients with HER2-positive breast cancer brain metastasis (BCBM) showed an intracranial response rate of 74.6% in patients who had not previously received radiation, and a 42.1% response rate in those who had progressed after radiation[34]. In the HER2CLIMB trial, the combination of tucatinib, trastuzumab, and capecitabine demonstrated a median PFS of 7.8 months, significantly outperforming the placebo group (5.6 months), with notable efficacy in the brain metastasis subgroup[35]. Another clinical study also confirmed the intracranial efficacy of the combination of pyrotinib and capecitabine in HER2-positive breast cancer brain metastasis (BCBM) patients. The study divided patients into three cohorts: those who had never received local radiotherapy, those with stable disease after local radiotherapy, and those with progression after local radiotherapy. The results showed that the central nervous system objective response rates (CNS-ORR) were 72.73%, 55.00%, and 42.86% in the three groups, with median progression-free survival (PFS) of 11.0, 8.4, and 5.2 months, respectively. Additionally, the treatment was well tolerated[36].These studies highlight the unique role of small molecule TKIs in the treatment of brain metastasis in HER2-positive breast cancer.

4.2 Prevention of Brain Metastasis

In addition to treating brain metastasis, preventing its occurrence is also an important research area. Some studies suggest that small molecule TKIs may have potential in preventing brain metastasis. For instance, clinical data from early HER2-positive breast cancer treatment revealed that the risk of central nervous system (CNS) recurrence was similar between the control and treatment groups, with an occurrence rate of about 2%. Notably, the use of neratinib during the extended treatment phase resulted in a 1.4% absolute reduction in CNS metastasis risk compared to the placebo group[37]. These findings suggest that neratinib's extended use can offer protection against CNS metastasis. Ongoing studies aim to further explore the mechanisms and clinical applications of small molecule TKIs in preventing brain metastasis, with the potential for early TKI use to become a focal point in the

management of advanced breast cancer.

5. Future Directions in HER2-Targeted Therapy

5.1 Development of New Targeted Drugs

With ongoing research into the HER2 signaling pathway, the development of new HER2-targeted drugs will be a key focus in the future. For example, trastuzumab deruxtecan (T-DXd), a novel antibody-drug conjugate (ADC), has shown significant efficacy in several clinical studies. Its high potency and favorable intracranial activity provide new strategies for treating HER2-positive breast cancer[38]. Other new targeted drugs, such as margetuximab and inritumomab, are also emerging. These drugs target the HER2 pathway through different mechanisms and may offer additional treatment options for HER2-positive breast cancer patients.

5.2 Exploration of Combination Therapy Strategies

Combination therapies represent an important development direction for HER2-positive breast cancer treatment. In addition to current regimens combining monoclonal antibodies with chemotherapy or small molecule TKIs, the combination of HER2-targeted drugs with other therapeutic modalities will become a research hotspot. Strategies combining HER2-targeted therapy with immune checkpoint inhibitors have shown preliminary efficacy in some clinical trials and may emerge as a new treatment approach. For example, the Neo-PATH study[39] aims to investigate the efficacy and safety

5.3 Personalized Treatment and Precision Medicine

With the development of molecular biology and genomics, personalized treatment has gradually become an important direction in the treatment of HER2-positive breast cancer. By precisely analyzing the molecular characteristics of tumors, tailored treatment plans can be provided for patients. For example, genetic testing based on liquid biopsy technology can detect tumor DNA in the patient's blood, helping to understand the tumor's genetic mutation types, thereby predicting treatment responses and the development of drug resistance. Future research will focus on exploring how to adjust treatment strategies according to the patient's specific genetic background and tumor characteristics, in order to improve treatment efficacy and reduce unnecessary side effects.

In addition, technologies for companion diagnostics (such as detecting HER2 amplification and mutations) will continue to develop, helping clinicians more accurately assess a patient's response to different treatments, thus further promoting the implementation of personalized therapies. Through these precision medicine approaches, HER2-positive breast cancer patients will receive more personalized, precise, and effective treatments.

6. Conclusion

The treatment of HER2-positive breast cancer has made significant progress, especially with the continuous development of targeted therapies and the introduction of new drugs. Existing treatment options, such as trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine, have significantly improved patients' survival rates and quality of life. However, as efficacy continues to improve, new challenges, such as drug resistance and brain metastasis, have emerged. These challenges require us to continually innovate and explore new treatment strategies.

In the future, the treatment of HER2-positive breast cancer will move towards more precise and personalized approaches. New targeted drugs, the combination of immunotherapies, the further promotion of individualized treatment, and the discovery of new molecular targets may provide more treatment options and longer survival periods for HER2-positive breast cancer patients. At the same time, preventing brain metastasis, addressing drug resistance, and optimizing existing treatment regimens will continue to be important areas of clinical research.

In summary, the treatment prospects for HER2-positive breast cancer are optimistic, but ongoing exploration and refinement are still required. With the progress of scientific research and the continuous accumulation of clinical practice, more effective treatments will emerge in the future, bringing better outcomes for patients.

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