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Advances in the Treatment of Triple-Positive Breast Cancer

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Abstract: Triple-positive breast cancer is a special type of breast cancer characterized by significant specificity in its clinical features and biological manifestations. Unlike the treatment strategies for simple hormone receptor (HR)-positive or human epidermal growth factor receptor 2 (HER2)-positive breast cancer, triple-positive breast cancer is sensitive to endocrine therapy, adjuvant therapy, and targeted therapy. With the in-depth study of the complex drug resistance mechanisms of triple-positive breast cancer, relevant treatment options are continuously optimized, providing new directions for the treatment of this disease.

Keywords: Triple-positive breast cancer; Treatment progress; Drug resistance mechanism; Endocrine therapy; Targeted therapy

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1. Introduction

Breast cancer is a common, clinically heterogeneous malignancy, mainly affecting female patients. It ranks among the leading causes of morbidity and mortality from malignancies in women [1]. In recent years, the epidemiological trend has been rising, making it one of the urgent problems to be solved in medical development. Triple-positive breast cancer is a special type of breast cancer molecular typing, characterized by the co-expression of simple hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2). Its pathological mechanism and epidemiological characteristics are not yet clear, and most pathological studies are invasive ductal carcinoma, which is prone to proximal and distal metastasis, and the disease prognosis is poor. Currently, research on the treatment of triple-positive breast cancer in China is still in the research stage, and conventional endocrine therapy has high drug resistance. There is some controversy among clinical scholars, and there is no unified standard for the treatment of triple-positive breast cancer. This article aims to provide a reference for the clinical treatment of triple-positive breast cancer by summarizing the current research status and known treatment results.

2. Clinical characteristics and drug resistance mechanisms of triple-positive breast cancer

Clinical studies have shown that triple-positive breast cancer accounts for approximately 15% of total breast cancers and 50% of HER2-positive breast cancers. The affected population is mainly aged between 45 and 75 [2]. This type of cancer is characterized by low differentiation of cancer tissue, high degree of malignancy, poor prognosis, and a higher mortality rate within the past five years. Triple-positive breast cancer is primarily treated with endocrine therapy. However, due to its low sensitivity to treatment, the short-term remission rate of solid tumors is significantly lower than that of patients with only HER2+, which is believed to be related to drug resistance. Scholars tend to think that the overexpression of HER2 mediates the downregulation of ER expression through MAPK and PI3K-Akr-mTOR stimulation, leading to difficulties in achieving ideal treatment effects and poor prognosis [3]. Both HER2 and ER signaling pathways play crucial roles in drug resistance, showing a negative correlation.

3. Progress in the treatment of triple-positive breast cancer

The complete remission rate of triple-positive breast cancer is relatively low, and there is a high risk of lymph node metastasis and cancer recurrence. Adjuvant and intensive adjuvant therapies can improve the prognosis of the disease [4]. Clinical scholars have adopted trastuzumab in the treatment of triple-positive breast cancer for patients who have not achieved complete remission after neoadjuvant chemotherapy, followed by TDM-1 treatment [5]. TDM-1 is the first ADC drug approved for the treatment of breast cancer, which can bind to HER2-expressing tumor cells and promote cancer cell apoptosis to exert a therapeutic effect.

3.1. Targeted combined endocrine therapy

There is a bidirectional crosstalk effect between ER and HER-2 signaling pathways. Treatment strategies targeting either pathway can lead to upregulation of the other pathway, resulting in resistance to treatment effects. Combination targeted therapy can effectively address endocrine and anti-HER-2 resistance, with a mechanism that simultaneously blocks both signaling pathways, providing a new clinical treatment direction. Scholars such as Zhang *et al.* [6] conducted a study analyzing trastuzumab combined with endocrine maintenance therapy for HR and HER-2 positive recurrent metastatic breast cancer. After achieving remission or stabilization of the disease with first-line trastuzumab combined with chemotherapy, trastuzumab combined with endocrine maintenance therapy was continued. The results showed that the median progression-free survival time for 31 patients with recurrent metastatic breast cancer undergoing maintenance therapy was 12.0 months (95% CI: 5.4–18.6 months). Five patients achieved complete remission after first-line chemotherapy with no evaluable lesions, and the remaining 26 patients were evaluable for short-term efficacy. The overall response and clinical benefit rates were 26.9% and 88.5%, respectively. Additionally, the adverse reactions caused by trastuzumab combined with endocrine maintenance therapy were controllable, with a 9.7% chance of inducing nausea and vomiting, a 16.1% chance of inducing hot flashes, and a 19.4% chance of inducing fatigue. This suggests that trastuzumab combined with endocrine maintenance therapy for HR+/HER-2+ metastatic breast cancer can further improve clinical benefits for patients.

3.2. PI3K-Akr-mTOR inhibitors

The PI3K-Akr-mTOR signaling pathway has been a hot topic in clinical research for targeted therapies in recent years and has been included by the US Food and Drug Administration as a treatment for breast cancer. Commonly used clinical inhibitors of the PI3K-Akr-mTOR signaling pathway include mTOR inhibitors, such as everolimus, and PI3K inhibitors, such as alpelisib. Everolimus, an mTOR inhibitor, is a novel drug designed to address endocrine therapy resistance. Zhang *et al.* studied the mechanism and combined effect of everolimus and bicalutamide on the breast cancer cell line MDA-MB-453 [7]. Western blot was used to detect changes in the expression of mTOR, p-mTOR, and p-S6 in breast cancer cell lines before and after bicalutamide treatment. Transwell migration and invasion assays were used to detect changes in cell activity before and after bicalutamide treatment. The MTT method was used to assess the effect of everolimus combined with bicalutamide on the proliferation of the MDA-MB-453 breast cancer cell line. The *Q* value was calculated using the Jin Zhengjun method to evaluate the inhibitory effect of the combination on the MDA-MB-453 breast cancer cell line. Experimental results showed that the proliferation of the MDA-MB-453 cell line was inhibited after treatment with bicalutamide combined with everolimus, and the *Q* value was greater than 1.15 at all concentrations, confirming that bicalutamide combined with everolimus can synergistically inhibit the proliferation of AR-positive breast cancer cells.

Alpelisib is often used in combination with TDM-1 and has achieved good results in the treatment of HER2-positive breast cancer [8]. According to research by Chen [8], breast cancer patients with different genetic structures are prone to mutations in the phosphatidylinositol-3-kinase catalytic σ subunit (*PIK3CA*). The mutation rate of the *PIK3CA* gene in HR+/HER2- breast cancer patients is about 40%. Alpelisib, developed by Novartis in Switzerland, is a PI3K inhibitor that can inhibit the PI3K enzyme subunit-encoding protein, targeting the *PIK3CA* gene mutation in breast cancer. It plays a significant role in the treatment and prognosis of patients with HR+/HER2- advanced or metastatic breast cancer and can significantly prolong the disease-free survival of breast cancer patients. It also has the same effect against HER2 resistance.

3.3. CDK4/6 inhibitors

In the treatment of triple-positive breast cancer, CDK4/6 inhibitors are mainly used in combination with anti-HER2 drugs. With a wide range of applications, they are gradually being applied to the treatment of other types of advanced breast cancer patients. Commonly used CDK4/6 inhibitors such as palbociclib have been studied by scholars such as Chen *et al.* [9]. The combination of palbociclib, letrozole, and fulvestrant was used to treat advanced HR+/HER2- breast cancer [9]. The results showed that the objective response rate (ORR) and disease control rate (DCR) were 11.29% and 82.26%, respectively. After treatment, carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), and carbohydrate antigen 125 (CA125) were significantly reduced to 19.49 ± 6.67 ng/mL, 11.54 ± 3.34 U/mL, and 43.34 ± 17.28 U/mL, respectively. After treatment, $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were 49.98 ± 6.90%, 31.02 ± 7.00%, 26.38 ± 3.35%, and 1.18 ± 0.39, respectively. The median progression-free survival and overall survival were 20 months (95% CI: 18.87–21.14) and 25 months (95% CI: 24.41–25.59), respectively. This confirms that palbociclib has a good clinical effect in advanced HR+/HER2- breast cancer, further regulating tumor marker levels.

3.4. Salvage therapy

For patients with advanced breast cancer who have metastatic lesions or cancer recurrence, clinical medication

should be comprehensively selected based on the location and pathological staging of the tumor. Dual-targeted combination chemotherapy is recommended. Zhu's [10] trial showed that the combination of pertuzumab and trastuzumab for the treatment of HER-2 positive breast cancer achieved a high ORR, with decreased levels of serum CA125, CA153, and TK-1, and reduced metastasis rate. This indicates that dual-targeted combination chemotherapy can lower patients' tumor marker levels and reduce the risk of recurrence and metastasis.

4. New therapeutic approaches for triple-positive breast cancer

Currently, there are numerous clinical studies ongoing in China regarding triple-positive breast cancer. For example, triple therapy using CDK4/6 inhibitors combined with aromatase inhibitors and tyrosine kinase inhibitors is being investigated for the treatment of patients with HR+ and HER2 advanced breast cancer. This approach provides a new adjuvant treatment strategy for patients with metastatic breast cancer. Currently available data suggests that triple therapy has broad prospects in the future treatment of triple-positive breast cancer, potentially offering more benefits as a first-line treatment, pending further clinical investigation.

5. Conclusion and outlook

The clinical specificity of triple-positive breast cancer determines that its treatment differs significantly from other types of breast cancer. The efficacy of endocrine therapy is often poor. Therefore, it is necessary to broaden treatment approaches under traditional treatment concepts, strengthen research on adjuvant therapy and targeted therapy, and conduct in-depth analyses of different drug resistance mechanisms to reduce endocrine therapy resistance. With the in-depth development of clinical pharmacy in recent years, there has been an increase in research on targeted combined endocrine therapy regimens. More and more drugs are providing options to block ER and HER2 signaling pathways, and additional treatments for drug-resistant triple-positive breast cancer are being developed, such as mTOP inhibitors and CDK4/6 inhibitors. These can be applied to patients with complex drug-resistant breast cancer, reversing endocrine resistance and making tumor cells more sensitive to endocrine therapy. It is believed that with the continuous development of the pharmaceutical industry, standardized treatment guidelines for triple-positive breast cancer will be released soon, providing direction for clinical first-line treatment, prolonging patient survival, and overcoming cancer.

Disclosure statement

The authors declare no conflict of interest.

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