

Progress in Target-Therapy with Breast Cancer

Ye Sun*

Harbin Medical University, Harbin, China

*Corresponding author: 2020157050@hrbmu.edu.cn

Abstract. With the increase of incidence rate of breast cancer, more attention has been paid to the treatment of this disease. This article mainly divides breast cancer into three negative breast cancer and HER2 overexpression breast cancer. Negative breast cancer can be divided into four subtypes, among which immunomodulatory pressure type is more sensitive to immunotherapy. The emergence of immunotherapy has brought new tumor treatment methods for breast cancer, mainly immune-checkpoint inhibitor therapy. The pathological complete response rate was significantly improved in the PD-1 drug development process in combination with neoadjuvant chemotherapy, and the combination therapy of monoclonal antibody and paclitaxel in the PD-L1 drug development process can significantly prolong survival rate. The combination of epeimab and navumab with paclitaxel in the treatment of early triple negative breast cancer is expected to improve ORR and PCR rates. This article briefly describes the development process of targeted therapy for human epidermal growth factor receptor 2, indicating that anti HER2 targeted therapy has entered the era of antibody drug conjugates. At the same time, the different clinical research and development status of PD-1 inhibitor, PD-L1 inhibitor and CTLA-4 inhibitor during immunotherapy also tells us that in the process of treating breast cancer, combined chemotherapy and targeted treatment are more conducive to improving the prognosis and meeting the requirements of patients to improve their quality of life.

Keywords: Breast cancer; immune-checkpoint; PD-L1.

1. Introduction

The data from the International Cancer Agency of the World Health Organization, there was 2.26 million new cases and 685000 deaths from breast cancer in the world in 2020, ranking first in the global incidence rate and mortality of female cancer. In addition, a study conducted by the International Family Planning Association (IPPF) shows that the global incidence rate of breast cancer increases by about 51 cases every year for every 1 million people. Breast cancer is a malignant tumor caused by uncontrollable reproduction of breast epithelial cells under the behavior of a various of carcinogens [1]. The breast is not an essential organ to maintain human life activities. Breast cancer in situ is not fatal, but malignant breast cancer cells have lost the characteristics of normal cells, the connection between cells is loose which makes them easy to fall. Breast lumps, nipple discharge, and enlarged axillary lymph nodes are often the early symptoms [2]. However, once cancer cells fall off, free cancer cells can spread throughout the body with blood or lymph, called metastasis, causing multiple organ diseases and endangering life. Thus, breast cancer has become a comply happened tumor, endangering women's physical and mental health.

The incidence rate of breast cancer has been on the rise, and has become one of the women's health problems concerned by the world. According to research, the gradual increase of incidence rate of breast cancer is related to factors such as changes in modern lifestyle and unbalanced nutritional structure. However, with the improvement of breast cancer screening technology, the incidence of early breast cancer is also rising. In terms of influencing factors, breast cancer mainly occurs in women, which may be related to the high level of estrogen. Estrogen is a carcinogen, and long-term high-level estrogen is likely to lead to malignant changes in breast cells. In addition, the rich female breast tissue also led to a higher incidence of breast cancer in women. Breast cancer mainly occurs in women over 50 years old after menopause. The risk of breast cancer is higher, which may be related to the decline of ovarian function and estrogen level after menopause. Genetic factors also determine the incidence rate of breast cancer. Studies have found that BRCA1 and BRCA2 gene mutations are related because these two genes encode proteins in the process of DNA repair and breast cancer

inhibition, so when mutations occur, the function of proteins will be damaged, and the incidence rate of breast cancer will rise. The influence of environmental factors cannot be ignored. Lifestyle habits such as smoking, drinking, obesity, and lack of exercise will lead to an increase in the incidence of breast cancer. Frequent exposure to radiation and chemicals. Long-term use of female hormones, long-term use of birth control pills, and hormone replacement therapy will all increase the risk of breast cancer [3].

Triple negative breast cancer (TNBC) accounts for about 15% of all breast cancer, and is considered as a special molecular type of breast cancer. Patients usually have a poor prognosis and a high risk of recurrence and metastasis. The traditional TNBC mainly refers to breast cancer with negative expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 [4]. After many studies, it mainly includes four subtypes: immune regulatory type, luminal androgen receptor type, mesenchymal like cell type, and mesenchymal stem cell type. Mesenchymal like cell type: It is characterized by strong invasion and easy metastasis, and the image shows the morphology of metaplastic breast cancer; Pathological examination shows differentiation of sarcomatous and squamous epithelioid lesions. Due to the low adhesion of tumor cells, the incidence of distant metastasis is high. Mesenchymal stem cell type: characterized by cancer cells possessing stem cell properties. Due to its multicellular differentiation function, it has a high recurrence rate and high invasiveness and metastasis. Imaging examination shows spiculated and pointed shadows, irregular tissue morphology, smooth edges, and rapid disease progression. Androgen receptor body type: High density shadows can be seen on imaging, and the pathological tissue morphology is irregular with tissue calcification. The probability of distant metastasis of lymphatic tissue is high, and the lesion tissue occupies a significant space and has a large volume. Immunomodulatory type: Imaging is characterized by edema caused by local inflammation and infiltration of immune cells into tumor lesions. Due to the delayed activation of the immune system, the symptom response during the onset of the disease is not obvious or the symptom response is more insidious than other types [4]. Among them, the immunomodulatory subtypes have a better prognosis and are more sensitive to immunosuppressive therapy. The main mechanism of this process is to change the tumor microenvironment, to reactivate the body's immune function and kill tumor cells. The immune system can recognize, kill, and promptly clear abnormal proliferative cells in the body. Tumor cells, as abnormal cells, can be recognized and cleared by the immune system under normal circumstances. However, a small number of tumor cells can affect and alter their immune microenvironment, leading to immune escape and tumor occurrence and development. Immunotherapy is the process of improving the ineffective tumor immune microenvironment, allowing the immune system to regain its anticancer effects in the tumor microenvironment, achieving the goal of controlling and even eliminating tumor cells. The emergence of immunotherapy has brought new treatment methods for tumors in addition to surgery, chemotherapy, radiation therapy, endocrine and targeted therapy. Immunotherapy includes various strategies, including cell adoptive therapy, tumor vaccines, oncolytic viruses, immune checkpoint inhibitors (ICI), etc., and current popular research has focused on ICI, especially programmed death receptor 1 (PD-1)/programmed death receptor ligand 1 (PD-L1) inhibitors.

Twenty to twenty-five percent of all cases of breast cancer are positive for the human epidermal growth factor receptor 2 (HER2). Tyrosine kinase activity is present in the transmembrane protein HER2. Breast cancer with overexpression of HER2 is more incurable and has a dismal prognosis. The development of medications that target the HER2 has been ongoing since the 21st century which provided more treatment options for HER2 positive breast cancer patients and significantly improved their survival prognosis. Targeted therapy refers to the specific binding of drugs to carcinogenic sites when they enter the body, resulting in tumor cell specific death without affecting normal tissue cells around the tumor. Targeted therapy aims to activate receptor genes in estrogen receptor negative cells or introduce active genes into breast cancer cells. The current targeted drugs for HER2 mainly include monoclonal antibody drugs such as trastuzumab and pertuzumab, small molecule tyrosine kinase

inhibitors such as lapatinib and naratinib, and antibody drug conjugates such as T-DM1 and T-DXd. These drugs play extremely important roles in different disease stages.

2. Treatment with Breast Cancer

It is generally believed that overexpression of Her-2 indicates rapid proliferation of tumor cells. This is because Her-2 plays a crucial role in the growth and development of normal cells. Normal cells contain about 20000 Her-2 receptors, while some tumor cells contain more than 2 million (more than 100 times) Her-2 receptors. This phenomenon is called overexpression of Her-2 receptors, which is generally seen in about 30% of patients with metastatic breast cancer. Her-2 positive tumor cells exhibit higher growth stimulating activity than normal cells, leading to rapid tumor growth and spread. Her2 is typically expressed in epithelial cells of the breast and skin, as well as in the gastrointestinal, reproductive, respiratory, and urinary tracts. Monoclonal antibodies such as trastuzumab, pertuzumab, and dexmedetozumab play important roles as HER2 receptor inhibitors in the Breast cancer with over expression of HER2. TNBC does not express Her-2 and cannot be treated with targeted therapy against Her-2. Therefore, searching for other available targets and monoclonal antibodies is an important way to treat TNBC. PD-1 and PD-L1 inhibitors, as one of the most common immune checkpoint inhibitors, have shown significant therapeutic effects in immunotherapy of tumors, including urothelial tumors, non-small cell lung cancer, and melanoma. Breast cancer has long been considered as a non-immune tumor. However, new research has found that the expression level and activity of PD-L1 and tumor infiltrating lymphocytes (TILs) in patients with TNBC are significantly higher than those in other subtypes of breast cancer, indicating that TNBC has a strong immune focus and can also be used for anti PD-1 and PD-L1 treatment. And tumor cells disrupt immune balance by expressing PD-L1, inducing evasion of host immune response. PD-1 and/or PD-L1 inhibitors, as common immune checkpoint pathways, can maintain normal immune function by regulating T lymphocyte activation [5].

2.1. Targeted Therapy of Anti Human Epidermal Growth Factor Receptor 2

In 1998, the world's first anti HER2 monoclonal antibody trastuzumab came out, reversing the natural process of poor prognosis of HER2 positive advanced breast cancer, and opening a new era of anti HER2 targeted treatment of breast cancer [6]. The idea behind trastuzumab is that it is the first monoclonal antibody to be humanized for HER2+ and has achieved success in treating HER2+BC. Trastuzumab binds to the extracellular domain (ECD) of HER2, preventing cell cycle arrest, blocking the intracellular HER2 signaling pathway, and causing antibody-dependent cytotoxicity (ADCC). The efficacy of trastuzumab partially depends on the ADCC through its Fc domain. Patients respond more strongly to trastuzumab if they have immune effector cells (dendritic cells or natural killer cells) that bind more firmly to the Fc domain. In 2007, the first small molecule tyrosine kinase inhibitors (TKI) targeting HER2 came out, followed by nelatinib, pyrrolitinib, and tucatinib, bringing more drug choices to HER2 positive breast cancer patients, and achieving the TKI era of anti HER2 treatment. In 2012, the CLEOPATRA study was launched. In contrast to trastuzumab alone, the coadministration of pertuzumab and trastuzumab has demonstrated enhanced efficacy in prolonging overall survival (OS) and progression-free survival (PFS) among patients with advanced HER2 positive breast cancer. Consequently, this combination therapy has been established as the new standard first-line treatment for HER2 positive advanced breast cancer. At the same time, Neo Sphere and APHINITY studies have successively confirmed the role of trapidual target in the new adjuvant and adjuvant treatment of HER2 positive early breast cancer, and the anti HER2 treatment has entered the era of trapidual target. In 2013, Enmetriazumab became the second-line standard treatment for HER2 positive advanced breast cancer by virtue of the dual benefits of PFS and OS in the EMILIA study; In 2022, Detriazumab successfully challenged Enmetriazumab in the DESTINY-Break03 study, iteratively updated to become the second-line treatment standard, bringing new hope to patients

with HER2 positive advanced breast cancer, and also indicating that anti HER2 targeted treatment will soon enter the era of antibody drug conjugate (ADC) [7].

2.2. PD-1 Inhibitor

The immune checkpoint inhibitor pembrolizumab achieved dual positive endpoints for PFS and OS in the KEYNOTE-355 study [8]. The FDA approved pembrolizumab combined with chemotherapy as the first-line treatment for advanced TNBC patients with a combined positive score (CPS) of PD-L1 and above. The KEYNOTE-522 study confirmed the efficacy of pembrolizumab in early neoadjuvant therapy for TNBC. As a result, pembrolizumab was approved by the US FDA and the National Medical Products Administration (NMPA) of China for use as a neoadjuvant therapy in early-stage high-risk TNBC patients with PD-L1 CPS of 20 and above, opening the way for immune checkpoint inhibitors to treat early TNBC [9].

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1, an IgG4 isotype antibody targeting PD-1 that activates the immune system's anti-cancer mechanism. It has been approved by the FDA for use in any metastatic solid tumor containing certain genetic abnormalities (microsatellite instability or mismatch repair defects), such as melanoma. And Nivolumab is a humanized monoclonal antibody that binds to PD-1. These two monoclonal antibodies competitively block their binding to PD-1 on T cells and collaborating with PD-L1 on tumor cells, thereby upregulating the immune response and killing abnormal tumor cells [10]. Nivolumab is a monoclonal antibody against PD-1. The results of the Nivolumab randomized trial (Phase II) conducted simultaneously in TNBC patients indicate that both chemotherapy and radiotherapy can achieve high anti-cancer response rates in initiating the tumor microenvironment. The study found that the efficacy and safety of Nivolumab, Pembrolizumab and neoadjuvant chemotherapy in the treatment of high-risk HR positive HER2 negative early breast cancer. Compared with the simple neoadjuvant chemotherapy, the immunecheckpoint inhibitor combined with neoadjuvant chemotherapy can significantly improve the pathological complete response (pCR) rate [11].

Atezolizumab, Avelumab, and Durvalumab are monoclonal antibodies targeting the transmembrane protein PD-L1 on tumor cells [12]. Atezolizumab selectively binds to PD-L1, while Avelumab and Durvalumab are human IgG1 monoclonal antibodies that are completely bound to PD-L1. A combination therapy consisting of Atezolizumab and nanoparticle albumin bound (NAB) paclitaxel is used to treat PD-L1 positive TNBC metastasis or unresectable locally advanced tumors [13]. This combination therapy can significantly prolong the progress of free survival and OS of PD-L1 positive patients, and has been approved by the FDA.

2.3. CTLA-4 Inhibitor

CTLA-4 antibody blocks Foxp3+regulatory T cells in the tumor microenvironment pathway, causing T cell expansion, enhancing tumor cell rejection, and inducing anti-tumor immunity. Ipilimumab is a CTLA-4 blocker. FDA-approved in 2011 for the management of metastatic melanoma, it has demonstrated potent and long-lasting anti-cancer therapeutic benefits, leading to tumor shrinkage and regression. In the experiment to explore the effectiveness and security of neoadjuvant ipilimumab and nivolumab addition to paclitaxel for the treatment of TNBC in its early stages (triple negative breast cancer) patients with poor anthracycline chemotherapy response, the study included three stage TNBC whose standard vertebra was ≥ 18 years old and had ≥ 15 mm tumor residue or 10mm tumor accompanied by a positive lymph node after four cycles of anthracycline treatment [14]. The patient received treatment with ipilimumab, nivolumab, and paclitaxel for 12 weeks before undergoing surgery. Continue treatment with nivolumab for 9 months after surgery. Complete pathological response (pCR) is the primary outcome, and objective response rate (ORR), pCR, and event free survival (EFS), and overall survival (OS). A total of 34 patients were enrolled (median age 46.6 years, 47% lymph node positive, 26% PD-L1 positive). The results showed that the pCR rate (ypT0ypN0) was 24.2%, PD-L1+patients were 37.5%, and PD-L1- patients were 23%. The

pCR rate of patients with poor response to anthracycline drugs (<50% tumor reduction) was 18.8% (95% CI, 8.52-75.51).

The breast ORR of all evaluable patients was 57.6%, with 43.7% having poor response. The number of patients with residual cancer burden (RCB) levels 0, 1, 2, and 3 was 8 (24%), 1 (3%), 19 (57.5%), and 5 (15%), respectively. After a median follow-up of 14 months, the estimated EFS and OS at 12 months were 85% and 94%, respectively. The 12-month EFS of pCR and non pCR patients were 100% and 75%, respectively (HR 0.62). Research has shown that regardless of the PD-L1 status, the addition of ipilimumab and nivolumab to paclitaxel neoadjuvant therapy is expected to improve ORR and pCR rates [15].

3. Conclusions

According to the development process of PD-1 inhibitor drugs, the clinical and pathological complete response rates of nivolumab, pembrolizumab combined with neoadjuvant chemotherapy have significantly improved. In the development of PD-L1 inhibitor drugs, the combination therapy of Atezolizumab and nanoparticle albumin bound (NAB) paclitaxel can significantly prolong the overall survival rate of PD-L1 positive patients in the treatment of PD-L1 positive TNBC metastasis or unresectable locally advanced tumors. In the experiment of early TNBC patients with poor response to anthracycline chemotherapy with the combination of ipilimumab and nivolumab, data showed that the addition of ipilimumab and nivolumab in paclitaxel neoadjuvant therapy is expected to improve ORR and pCR rates. As the single drug efficacy does not meet clinical expectations, immunotherapy for breast cancer pays more attention to combination therapy, including combination chemotherapy, targeted therapy, and local radiotherapy. Some studies have also shown that trastuzumab combined with capecitabine has a good effect on reducing the level of inflammatory factors, reducing the occurrence of adverse reactions, and improving the quality of life in breast cancer patients. In view of the high recurrence rate and poor prognosis of triple negative breast cancer, it is difficult to select conventional chemotherapy to meet the patient's needs. The low incidence of adverse reactions during the treatment of various combination drugs suggests that the combination treatment of breast cancer is safe and reliable.

References

- [1] Xu H, Xu B. Breast cancer: Epidemiology, risk factors and screening. *Chinese Journal of Cancer Research*, 2023, 35(06): 565-583.
- [2] Zhang M, Qiu J, Qu S, et al. Clinical observation of docetaxel combined with capecitabine neoadjuvant chemotherapy in the treatment of locally advanced breast cancer, *The Chinese German Journal of Clinical Oncology*, 2014, 13 (11): 515-517
- [3] Zhou Jun. Epidemiology of breast cancer, *Healthy Life*, 2019 (11): 3.
- [4] Lin D, Thompson CL, Demalis A, et al. Association between pre-diagnosis recreational physical activity and risk of breast cancer recurrence: the California Teachers Study. *Cancer Causes Control*. Published online April 13, 2024.
- [5] Li Xiaoyu, Li Yepeng, Tan Zhongqiu Research progress of immunotherapy in clinical treatment of breast cancer, *Journal of Guangxi Medical University*, 2023, 40 (05): 891-898.
- [6] Sun Lin. Correlation analysis of preoperative inflammatory factor ratio, prognosis and clinicopathological characteristics of breast cancer patients. *Jilin University*, 2023.
- [7] Huang Xiang, Yin Yongmei Little by little, little by little, a prairie fire - progress and prospect of drug therapy for breast cancer, *Pharmaceutical Progress*, 2024, 48 (02): 81-84.
- [8] Li Ping, Zhu Chengjun, Sun Yue, et al. Analysis of the Phase III clinical study of triple negative breast cancer with immuncheckpoint inhibitors. *China Clinical Research*, 2022, 35 (09): 1205-1210.
- [9] He Lihua, Zhu Xiuzhi, Jiang Yizhou Research progress in immunotherapy of triple negative breast cancer, *Chinese Journal of Clinical Pharmacology and Therapeutics*, 2023, 28 (08): 842-853

- [10] Lu Y, Chen Y, Hou G, et al. Zinc-Iron Bimetallic Peroxides Modulate the Tumor Stromal Microenvironment and Enhance Cell Immunogenicity for Enhanced Breast Cancer Immunotherapy Therapy. *ACS nano*, 2024,
- [11] Zhang Fang Research progress of neoadjuvant chemotherapy for triple negative breast cancer, *Chinese Journal of Metallurgical Industry Medicine*, 2024, 41 (02): 137-13.
- [12] Fantacuzzi M, Paciotti R, Agamennone M. A Comprehensive Computational Insight into the PD-L1 Binding to PD-1 and Small Molecules. *Pharmaceuticals*, 2024, 17(3).
- [13] Chen Y. Based on immune checkpoint inhibitor to improve cancer treatment, Wuhan Zhicheng Times Cultural Development Co., Ltd. Proceedings of 3rd International Conference on Medical Imaging, Sanitation and Biological Pharmacy (MISBP 2022). Department of Medical, Jiangsu University; 2022:9.
- [14] Rudolf N, Gabriele S, Gert A, et al. PITX2 DNA-Methylation: Predictive versus Prognostic Value for Anthracycline-Based Chemotherapy in Triple-Negative Breast Cancer Patients. *Breast care (Basel, Switzerland)*, 2021, 16(5):523-531.
- [15] Sherene Loi, Prudence A. Francis, Nicholas Zdenkowski, Val GebSKI, Stephen B. Fox, Michelle White, Belinda Emma Kiely, Natasha E. Woodward, Rina Hui, Andrew David Redfern, Raewyn Calvert, Lauren Rennie, Frances M. Boyle, Breast Cancer Trials-Australia and New Zealand. *Journal of Clinical Oncology* 2022 40:16_suppl, 602-602.