Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/73/2024.18879

Advances in the targeted therapy for breast cancer

Yaoyun Zhang

Department of Biological Science and Technology, Hunan Agricultural University, Changsha, 410125, China

Zyyztt2004@stu.hunau.edu.cn

Abstract. In 2022, 670000 people died because of breast cancer (BC). Notwithstanding their age and gender, women make up about half of the total number of instances of BC without any specific risk factors. In 157 out of 185 nations in 2022, BC will be the most frequent cancer among women. With the continuous progress of research, BC has achieved great breakthroughs, such as the introduction of BC immunotherapy, which is a revolutionary treatment for some patients; In addition is the introduction of antibody-coupled drugs (ADCs) that can target the delivery of potent chemotherapy drugs into breast cancer cells. This paper analyzes the treatment of some targets in BC, and obtains the application effect of some new drugs in breast cancer, which buys time for clinical treatment such as surgery. However, there are still some drugs with unclear effect on breast cancer treatment, and some drugs are only used alone. Future studies can pay more attention to the aspects of drug combination therapy.

Keywords: Breast cancer, HER2, PAPR, Olaparib, talazoparib.

1. Introduction

The malignant proliferation of mammary gland epithelial tissue causes breast cancer (BC), a type of tumor illness that has surpassed lung cancer as one of most common cancer worldwide [1].A vast number of young cancer cells with unlimited growth, disorderly crowding, squeezing and destroying the surrounding normal tissues, and eroding the normal tissue structure of the breast are the histological signs of breast cancer [2].Given the ongoing advancements in science and technology, there are more and more means of cancer examination, and the diagnosis accuracy of BC is getting higher and higher. Currently, treatments for BC include surgery, radiation and chemotherapy. Among them, surgery is the main treatment, combined with radiotherapy, chemotherapy and other methods [3], the specific treatment plan depends on the stage and type of BC. However, surgical treatment (that is, removal of the breast) although the treatment effect is relatively good, but there are still some drawbacks, for example, women will lose their most concerned about the aesthetic organs, will cause a certain burden on life and psychology. In addition, nausea, vomiting, loss of appetite, weight loss, fatigue, and a low blood count, which can lead to anemia, are common side effects of chemotherapy. With the advancement of technology, targeted therapy has entered our field of vision. Inhibiting specific targets/molecules that contribute to tumor progression is the primary objective of targeted therapy [4].

At present, the targeted therapies are HER2, PARP inhibitors and immune checkpoint inhibitors. This article will focus on the above treatment and related drug treatment data, to provide direction for clinical treatment.

DOI: 10.54254/2753-8818/73/2024.18879

2. Treatment with HER2 Targets

Her2-positive BC is responsible for approximately 20% to 25% of all BC cases. Human epidermal growth factor receptor-2 (HER2) amplification, which occurs either through HER2 gene amplification or protein overexpression, is an important factor for the high aggressiveness and poor prognosis of HER2-positive BC. Patients' prognosis and survival rates have risen significantly after anti-HER2-targeting medications became available. The prognosis for patients with this genetic subtype of BC has greatly improved with the discovery and use of anti-HER2 therapy medications. Traditional macromolecular antibodies, small molecular tyrosine kinase inhibitor (TKI) and antibody-drug conjugate (ADC) drugs are the main classes of drugs used in anti-her2 targeted therapy. Targeting HER2 extracellular domains, macromolecular antibodies, such pertuzumab and trastuzumab, bind to HER2's extracellular domains (ECD) IV and II, obstruct the intracellular HER2 signaling pathway, stop the cell cycle, and cause cytotoxicity that is dependent on antiboy activity; TKI is a small molecule that binds to the HER2 and other family members' intracellular tyrosine kinase domains. In order to stop phosphorylation and the propagation of downstream signaling pathways, it competes with ATP; ADC is composed of monoclonal antibodies and small molecules cytotoxic drugs coupled through the link. It targets tumor cells, specifically recognizes HER2 and antigens on their surface, initiates antibody-mediated endocytosis into the tumor cells, and then releases cytotoxin, killing the tumor cells. For HER2-positive BC, neoadjuvant therapy has been widely concerned and valued.

2.1. HER2-positive BC can benefit from double-target therapy during neoadjuvant therapy

Pertuzumab is utilized as the next monoclonal antibody in treating BC that is HER2-positive following trastuzumab. NeoSPHERE assessed the safety and effectiveness of four distinct neoadjuvant treatment combinations for patients with early-stage, inflammatory, or locally advanced HER2-positive BC: trastuzumab (H) + pertuzumab (P) + docetaxel (T). According to the data, there was no discernible rise in adverse responses, and the THP group outperformed the TH group in terms of bpCR (45.8% vs. 29%, P=0.0141) and tpCR (39.3% vs. 21.5%) [5]. Patients who achieved a complete response rate (pCR) with a combination of docetaxel, trastuzumab, and neoadjuvant pertuzumab were shown to have a favorable long-term prognosis, as demonstrated by 5-year PFS and disease-free survival (DFS) of 86% and 84%, respectively [6]. With the announcement of the results of NeoSPHERE and PONEY and other studies, the role and status of HP double target in early BC treated with neoadjuvant treatment that is HER2-positive have been clarified. However, how to optimize chemotherapy drugs to achieve the best therapeutic effect and relatively controllable toxicity of HP double target therapy patients has become a hot topic in this field. The first clinical trial to assess the combination of anthracycline-free chemotherapy with HP dual-target neoadjuvant treatment for those with early-stage HER2-positive BC is called TRAIN-2. Enrolled patients received six cycles of paclitaxel plus carboplatin or nine cycles of paclitaxel plus carboplatin after three rounds of 5-fluorouracil, epirubicin, and cyclophosphamide. In 2018, the study's principal outcome, the pCR data, were released: anthracycline/anthracycline free chemotherapy combined with trastuzumab + pertuzumab neoadjuvant therapy showed similar benefits (pCR 67% vs. 68%, P=0.95) [7]. ASCO reported the results of 3-year follow-up in 2020, 3-year EFS were 92.7% and 93.5%, and the three-year OS was 98.2% and 97.7%, correspondingly. The presence or absence of anthracene had no significant impact on EFS and OS of patients [6]. When it comes to safety, the anthracyclic regimen's hematological and cardiovascular toxicity is comparatively higher [8]. The combination of HP dual-target with non-anthracyclines can dramatically minimize toxicity while assuring good short- and long-term efficacy, according to follow-up results from the TRAIN-2 research [6].

2.2. ADC drugs in anti-HER2 therapy

In the therapy of anti-HER2, a new generation of ADC medications is being developed rapidly. In international settings, T-DM1, the first ADC drug licensed for the treatment of BC, is usually administered as an alternative therapy for advanced HER2-positive BC. Adjuvant therapy with T-DM1 is recommended for patients who do not achieve pCR after neoadjuvant therapy. Furthermore, in clinical

DOI: 10.54254/2753-8818/73/2024.18879

trials of neoadjuvant therapy for early HER2-positive BC, the PREDIX HER2 clinical study showed that neoadjuvant T-DM1 alone had equal pCR with a better safety profile [9]. Nevertheless, the pCR rate for HER2-positive BC treated with T-DM1+ pertuzumab as a neoadjuvant in the KRISTINE trial was lower than that of the TCbHP regimen [6]. According to long-term follow-up, the group getting systemic chemotherapy with trastuzumab and pertuzumab had better 3-year EFS than the group receiving T-DM1 and pertuzumab [10]. Neoadjuvant therapy for HER2-positive early BC with T-DM1 combined with pertuzumab is not advised since the heterogeneity of HER2 may influence T-DM1 combined with pertuzumab and result in a reduced pCR rate [11].

At present, HER2-positive BC which can be treated with neoadjuvant therapy is recommended as a priority of trepa dual-target chemotherapy. However, trastuzumab resistance occurs due to damage of HER2 binding sites, activation of downstream signal transduction pathways, amplification of HER2 gene and high protein expression. Therefore, combining other anti-HER2 drugs with trastuzumab complementary activity may be a solution. TKI drugs can enhance the efficacy of anti-HER2 monoclonal antibody by enhancing the antibody dependent cell-mediated cytotoxic effect and enhancing the expression of HER2, and the combination of strong and strong drugs can effectively overcome trastuzumab resistance.[6]

3. Treatment with PARP Inhibitors

Because BC is a malignant tumor, it must be classified into various subtypes according to the condition of hormone receptors (HR), such as progesterone and estrogen receptors (PR), and human epidermal growth factor receptor 2 (HER2). This will enable the choice of several treatment alternatives [12]. Because triple-negative BC lacks HER2 and HR expression, it is less responsive to hormone therapy and HER2-targeted treatments. BC susceptibility genes (BRCA) are important tumor suppressor genes, including BRCA1 and BRCA2. BRCA proteins are essential for homologous recombinant DNA repair pathways and are engaged in many important cell growth functions, such as DNA damage repair and proper cell growth. As of right now, mutations that cause BC are known to be associated with the BRCA1/2 gene. If so, the gene's capacity to stop tumor growth will be impaired, which would result in a noticeably increased risk of cancer [13]. Patients with gBRCA mutations that are toxic or potentially harmful for HER2-negative breast cancer may benefit from monotherapy with olaparib and talazoparib [14].

3.1. Olaparib in a phase 3 OlympiAD trial

Physicians randomly allocated patients in a 2:1 ratio to receive 300 mg of olaparib tablets twice daily or to receive single-agent conventional therapy of their choice (TPC) in the prospective Phase 3 investigation OlympiAD. The trial was double-blind and randomized [14]. The main purpose of the study was to compare olaparib with TPC in terms of progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and health-related quality of life (HRQoL) [15]. From this trial, it can be inferred that the olaparib group had a considerably longer median infinite PFS than the TPC group, and that the olaparib group also had a longer 48-month survival than the TPC group [14]. In patients with second- or third-line metastatic illness, olaparib was also more effective than TPC over the OS benefit period [14]. Olaparib had a higher ORR than TPC in blinded independent central review, investigator-assessed, and patients of visceral metastases [14]. Additionally, fewer patients in the olaparib group reported adverse events (AES) of grade 3 or higher than in the TPC group [14]. Among those on olaparib, the most frequent side effects were nausea, anemia, vomiting, etc. Anemia, neutropenia, exhaustion, and other AES were above grade 3 [14]. Because the accumulation of toxicity is not significant and olaparib dose interruption does not have a significant effect on the duration of treatment, few people will interrupt treatment of olaparib, but will manage toxicity through supportive therapy, dose interruption, and dose reduction, and thus continue treatment [14].

DOI: 10.54254/2753-8818/73/2024.18879

3.2. In the Phase 3 EMBRACA Trial, talazoparib

Physicians randomly allocated patients in EMBRACA, a prospective, multicenter, multi-country, double-blind, randomized Phase 3 trial, in a 2:1 fashion to receive 300 mg of talazoparib tablets once daily or single-agent conventional treatment (TPC) [14]. The purpose of this trial was to evaluate the efficacy and safety of TPC against olaparib in patients with gBRCA-mutated locally progressed or metastatic breast cancer. Additionally, differences in PFS, OS, ORR, and HRQoL were discussed. From this experiment, it may be inferred that the olaparib group had a considerably longer median infinite PFS than the TPC group, and that the olaparib group also had a higher 48-month survival than the TPC group [14]. Following several evaluations, there was no appreciable change in OS between the groups receiving talazoparib and TPC [14]. Compared to the TPC group, the group treated with talazoparib had a greater ORR, regardless of investigator assessment or in subgroups of TNBC and HR+ patients (with or without exposure to chemotherapy), with ORR more than twice as high in the investigator-assessed Talazoparib-treated group than in the TPC group [14]. In terms of HRQoL, patients in the talazoparib treatment group showed significant improvement and relieved symptoms such as pain and fatigue [14]. In addition, Comparing the talazoparib treatment group to TCP, there was a greater percentage of grade 3 or 4 hematologic AES and a lower percentage of grade 3 non-hematologic AES [3]. The most common AES in talazoparib are hematology, for example, anemia, neutropenia, and thrombocytopenia, with anemia accounting for more than half of these, which are usually grade 3. Non-blood AES is generally grade 1 or 2 and mainly includes fatigue, heartbreak, headache and hair loss [16,17]. Based on clinical findings, partial hematologic AES tend to stabilize at 25 weeks, while partial non-hematologic AES tend to stabilize at 50 weeks [14]. And the results suggest that supportive care can effectively control toxicity [14].

4. Treatment with immune checkpoint inhibitors

Triple negative breast cancer (TNBC) is a subtype of breast cancer that is expected to affect 15–24 percent of women with the disease; it tests negative for progesterone and HER2 [18]. Larger tumor volumes, higher tumor grades, increased risk of lymph node metastases, high invasiveness, strong heterogeneity, and ease of recurrence and metastasis are characteristics of TNBC, which is typically more common in young women. Other solid cancers have shown longer life times thanks to immunotherapy, it has prolonged the survival of other solid tumors, so there is a good prospect of development in TNBC treatment, among which immune checkpoint inhibitors (ICIs) are a drug with good therapeutic effect. ICIs boost the cytotoxicity and proliferation of tumor-infiltrating lymphocytes (TILs) by blocking immunosuppressive receptors. With PD-L1 (avelumab, durvalumab, atezolizumab), CTLA-4 (ipilimumab), and PD-1 (pembrolizumab, nivolumab) monoclonal antibodies, long-lasting responses have been demonstrated in a variety of tumor types [19].

4.1. ICIs Monotherapy

Avelumab and atezolizumab, two PD-L1 inhibitors, are also being investigated as ICI monotherapy for mTNBC. Both results—the low response rate seen in pretreatment metastatic disease and the restricted single-agent efficacy of ICIs in mTNBC are displayed in Table 1 [19]

Table 1. avelumab and atezolizumab are being explored as ICI monotherapy for mTNBC [19].

Experiment	Conclusion
The phase Ib JAVELIN trial (NCT01772004) Avelummab	Number of pretreated patients 58, ORR 5.2%
The phase I trial (NCT01375842) Atezolizumab	Number of pretreated patients 115, ORR 10%

4.2. ICIs combined with targeted therapy

The treatment effect of monotherapy is modest, so now the study of combination therapy is continuing.

ICIs in combination with small-molecule inhibitors of angiogenesisThe use of small molecule anti-angiogenesis drugs in combination with PD-1 monoclonal antibody retroline therapy has advanced

DOI: 10.54254/2753-8818/73/2024.18879

somewhat in the modern era.Apatinib's ORR was 43.3% when combined with carrilizumab, and its median progression-free survival was 3.7 months [20]. For immunomodulatory mTNBC, following treatment with a combination of famitinib, carrellizumab, and albumin-paclitaxe, the ORR was 81.3%, the median PFS was 13.6 months, and the length of remission was 14.9 months [21]

ICIs in combination with PARP inhibitors: TOPACIO/KEYNOTE-162 demonstrated that for second-line and later advanced TNBC, the overall ORR and disease control rate (DCR) of pabolizumab in combination with nilapalib were 21% and 49%, respectively. Subgroup analysis showed that patients with BRCA mutations had a significantly higher ORR compared to wild-type (47% vs. 11%), whereas patients with PD-L1-positive patients had an ORR of 32% compared to 8% in PD-L1-negative patients [22]. The I-SPY2 research examined the effectiveness of paclitaxel alone against duvaliuzumab with olaparib and paclitaxel as neoadjuvant therapy in patients with HER-2-negative BC. The combination treatment group in the TNBC subgroup had a pCR rate of 47%, while the group receiving paclitaxel monotherapy had a pCR rate of 27% [23] Therefore, at present, the study of PAPR inhibitor combined with ICIs in the late treatment is actively carried out.

ICI Conjugate Compound: Datopotamab deruxtecan, also known as Dato-DXd, is an ADC-class medication that combines a topoisomerase I inhibitor with human TROP-2 targeting. At the 2022 European Society of Medical Oncology Annual Meeting on BC, the BEGONIA study, which investigated the efficacy and safety of DATO-DXD plus duvaliuzumab as a first-line treatment for metastatic BC, presented its preliminary results. For analysis, an overall of 29 cases were enrolled. Two patients had a full response with adequate safety, and the ORR was 74% [5]. At present, the research in this area is still very limited, but it is still being studied in an orderly manner.

5. Conclusion

This paper focuses on the targeted therapy of HER2 and BRCA-induced breast cancer, and discusses in detail the HER2 targets, PARP inhibitors and immune checkpoint inhibitors respectively. Among them, dual-targeted medications provide a more potent therapeutic effect than standard medications in the treatment of HER2-positive BC, and novel ADC medicines are continuously being developed. In addition, treatment options for triple-negative BC are as follows: employing PAPRi to prevent the growth of tumor cells or using immunosuppressive receptors to increase TIL cytotoxicity and proliferation. Chemotherapy, radiation therapy, and surgery continue to be the cornerstones of BC treatment today. However, the majority of these approaches are limited to treating early-stage breast cancer; managing advanced cases and metastases remains a challenge in clinical settings. This article discusses targeted therapy, which offers a novel concept for the clinical treatment of BC. Through targeted therapy, the development of BC can be delayed or inhibited to buy time for surgery and other treatment programs. However, at present, targeted therapy still has certain limitations, many drugs are still unknown, we do not know its efficacy, so now still need to continue to explore. With the ongoing advancements in science and technology, targeted therapy will be constantly updated to strive for more opportunities for cancer patients.

References

[1] Xia, C., Dong, X., Li, H., Cao, M., Sun, D., He, S., Yang, F., Yan, X., Zhang, S., Li, N., & Chen, W. (2022). Cancer statistics in China and the United States, 2022: Profiles, trends, and determinants. Chinese Medical Journal (English), 135(5), 584-590.

[2] Shen, K. K., Yuan, J. J., Liu, Y. F., Li, C., & Guo, Y. J. (2017). Application of three-dimensional shear wave elastography in the differential diagnosis of benign and malignant breast masses. Chinese Journal of Ultrasound Imaging, 1057-1061. (in Chinese)

[3] Ben-Dror, J., Shalamov, M., & Sonnenblick, A. (2022). The history of early breast cancer treatment. Genes (Basel), 13(6), 960.

[4] Ye, F., Dewanjee, S., Li, Y., Jha, N. K., Chen, Z. S., Kumar, A., Vishakha, Behl, T., Jha, S. K., & Tang, H. (2023). Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Molecular Cancer, 22(1), 105.

[5] Gianni, L., Pienkowski, T., Im, Y. H., et al. (2012). Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncology, 13(1), 25-32.
[6] Liu, Y., & Yang, C. (2024). Strategy and status of neoadjuvant therapy for HER2-positive breast cancer. Cancer Research on Prevention and Treatment, 51(1), 12-15.
[7] van Ramshorst, M. S., van der Voort, A., et al. (2018). Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncology, 19(12), 1630-1640.
[8] Wang, H., & Mao, X. (2020). Evaluation of the efficacy of neoadjuvant chemotherapy for breast cancer. Drug Design, Development and Therapy, 2423-2433.
[9] Hatschek, T., Foukakis, T., Bjöhle, J., et al. (2021). Neoadjuvant trastuzumab, pertuzumab, and docetaxel vs trastuzumab emtansine in patients with ERBB2-positive breast cancer: A phase 2 randomized clinical trial. JAMA Oncology, 7(9), 1360-1367.
[10] Hurvitz, S. A., Martin, M., Jung, K. H., et al. (2019). Neoadjuvant trastuzumab emtansine and pertuzumab in human epidermal growth factor receptor 2-positive breast cancer: Three-year outcomes from the phase III KRISTINE study. Journal of Clinical Oncology, 37(25), 2206-2216.
[11] Filho, O. M., Viale, G., Stein, S., et al. (2021). Impact of HER2 heterogeneity on treatment response of early-stage HER2-positive breast cancer: Phase II neoadjuvant clinical trial of T-DM1 combined with pertuzumab. Cancer Discovery, 11(10), 2474-2487.
[12] Wilcock, P., & Webster, R. M. (2021). The breast cancer drug market. Nature Reviews Drug Discovery, 20(5), 339-340.
[13] Lan, T. Q., & Wei, J. C. (2024). Current status and prospects of PARP inhibitors in breast cancer applications. Shandong Chemical Industry, 53(12), 89-91. (in Chinese)
[14] Cortesi, L., Rugo, H. S., & Jackisch, C. (2021). An overview of PARP inhibitors for the treatment of breast cancer. Targeted Oncology, 16(3), 255-282.
[15] Robson, M., Im, S. A., Senkus, E., Xu, B., Domchek, S. M., Masuda, N., Delaloge, S., Li, W., Tung, N., Armstrong, A., Wu, W., Goessl, C., Runswick, S., & Conte, P. (2017). Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. New England Journal of Medicine, 377(6), 523-533.
[16] Litton, J. K., Rugo, H. S., Ettl, J., et al. (2018). Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. New England Journal of Medicine, 379(8), 753-763.
[17] Hurvitz, S. A., Gonçalves, A., Rugo, H. S., et al. (2020). Talazoparib in patients with a germline BRCA-mutated advanced breast cancer: Detailed safety analyses from the phase III EMBRACA trial. Oncologist, 25(3), e439-e450.
[18] Bianchini, G., De Angelis, C., et al. (2022). Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nature Reviews Clinical Oncology, 19(2), 91-113.
[19] Keenan, T. E., & Tolaney, S. M. (2020). Role of immunotherapy in triple-negative breast cancer. Journal of the National Comprehensive Cancer Network, 18(4), 479-489.
[20] Liu, J., Liu, Q., Li, Y., et al. (2020). Efficacy and safety of camrelizumab combined with apatinib in advanced triple-negative breast cancer: An open-label phase II trial. Journal for ImmunoTherapy of Cancer, 8(1), e000696.
[21] Chen, L., Jiang, Y. Z., Wu, S. Y., et al. (2022). Famitinib with camrelizumab and nab-paclitaxel for advanced immunomodulatory triple-negative breast cancer (FUTURE-C-Plus): An open-label, single-arm, phase II trial. Clinical Cancer Research, 28(13), 2807-2817.
[22] Hu, N. L., Sun, M. X., & Wu, S. K. (2022). Research progress on immune checkpoint inhibitors in triple-negative breast cancer. Chinese Medical Journal, 102(38), 4. (in Chinese)

DOI: 10.54254/2753-8818/73/2024.18879

[23] Pusztai, L., Yau, C., Wolf, D. M., et al. (2021). Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. Cancer Cell, 39(7), 989-998.e5.