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Progress in the treatment of advanced triple-negative breast cancer

Hao Zhao[1,a], Xie Li[2,b], Wu Yingying[1,c,*]

[1]Department of Oncology, The Second Naval Hospital of the Southern Theater Command of PLA, Sanya, China
[2]Department of Anesthesiology, Qilu Hospital of Shandong University Dezhou Hospital, Dezhou, China
[a]18689567234@163.com, [b]103540325@qq.com, [c]hzhhzhhzhhzhhzh@163.com
[*]Corresponding author

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Abstract: Three negative breast cancer (TNBC) refers to breast cancer with negative estrogen receptor, progesterone receptor and proto oncogene human epidermal growth factor receptor-2 in immunohistochemical examination of cancer tissue. It is a molecular subtype of breast cancer, with poor histopathological grading, high malignancy, strong invasion, prone to visceral metastasis and brain metastasis, high recurrence rate and strong heterogeneity. Due to its unique biological behavior and clinical pathological characteristics, there are still many deficiencies in treatment methods, and its prognosis is worse than other types. In recent years, with the discovery of special targets and the invention of targeted, immune and antibody conjugated drugs, precision therapy drugs have been gradually applied to the treatment of advanced triple negative breast cancer, which has the characteristics of specificity, efficiency, safety, etc. In traditional Chinese medicine, breast cancer belongs to the category of "milk rock". The treatment is guided by the idea of relative unity of form and spirit, and the principle of combining strengthening the body and expelling pathogens is used to improve the symptoms of patients. These different drugs have shown good anti-tumor activity when used for advanced triple negative breast cancer.

1. Introduction

Three negative breast cancer (TNBC) refers to breast cancer (BC) with negative estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2). It is common in young and obese women. The average age of onset is 53 years old[1], accounting for 15% to 20% of BC[2]. Most patients relapse within 1 to 2 years after diagnosis. Burstein MD divides it into intraluminal androgen receptor type, mesenchymal type, basal-like immunosuppressive type, and basal-like immune activation type, among which the prognosis of the basal-like immune activation type is the best, while the prognosis of the basal-like immunosuppressive type is the worst, and tumor-infiltrating lymphocytes in TNBC are associated with prognosis and efficacy[3].

Advanced triple negative breast cancer (aTNBC) includes locally advanced triple negative breast cancer (laTNBC) and recurrent or metastatic triple negative breast cancer (mTNBC).

In recent years, with the continuous deepening of medical research and the development of science and technology, precision therapy has taken its place in the treatment plan for patients with aTNBC. Its high specificity, efficiency, and safety have prolonged the survival period and improved the quality of life for patients with aTNBC. At the same time, with the deepening of the research on immunotherapy, the role of immunotherapy in breast cancer has gradually been paid attention to. Common immune checkpoint inhibitors include PD-1 inhibitors and CTLA-4 inhibitors, of which PD-1 inhibitors include PD-1 antibodies and PD-L1 antibodies. Compared with other molecular subtypes of breast cancer, the expression level and intensity of tumor infiltrating lymphocytes (TILs) of advanced TNBC are higher, and PD-L1 is mostly highly expressed, so it is speculated that it is most likely to benefit from immunotherapy.

Traditional Chinese medicine believes that breast cancer belongs to the category of "breast rock" in traditional Chinese medicine. The treatment is guided by the idea of relative unity of form and spirit[4]. The principle is to combine the strengthening of the body and the elimination of pathogens. It can improve the immunity of patients, reduce the adverse reactions of radiotherapy and chemotherapy, reduce tumor recurrence and metastasis, prolong the survival period of tumor patients and improve the quality of life of patients. Given the diversity of treatment options for advanced triple-negative breast cancer, the current application of aTNBC treatment is reviewed as follows.

2. Application of targeted drugs in the treatment of triple negative breast cancer

Targeted therapy is a method of treating cancer at the cellular and molecular level by designing specific drugs that target tumor cell marker molecules. It achieves the goal of treating cancer by interfering with tumor cell cycle, inhibiting tumor cell proliferation and metastasis, inducing tumor cell differentiation and apoptosis, and inhibiting tumor angiogenesis. Because it does not affect normal tissue cells surrounding the tumor, targeted therapy drugs are also known as "biological missiles". Currently, there are two polyribonucleotide polymerase inhibitors (PARPi) olaparib and talazoparib, as well as two neurotrophic receptor tyrosine kinase (NTRK) gene fusion inhibitors larotatinib and entrectinib, which have been approved by the FDA for the treatment of aTNBC patients[5-6].

2.1 PARPi

PARP is a multifunctional enzyme that plays a key role in DNA single-strand damage repair through base repair mechanisms. BRCA gene of breast cancer is an important tumor suppressor gene, including BRCA1 and BRCA2, which are mainly involved in DNA double strand damage repair through homologous recombination repair (HRR) pathway[7]. About 75% of TNBC patients have BRCA1/2 mutations[2], which means that PARPi may have a strong killing effect on such tumors.

Olapanide is an orally active PARPi, which has single drug antitumor activity in patients with metastatic breast cancer with BRCA1/2 mutation[7]. Research confirms that compared to standard chemotherapy (drugs such as capecitabine), olaparib monotherapy prolongs the median progression-free survival (mPFS) of patients with BRCA-mutated HER2-negative MBC after chemotherapy, reducing the risk of disease progression (PD) or death by 42% and significantly increasing the objective response rate (ORR). In terms of safety, most adverse events (AEs) in the olaparib group were grade 1 or 2, and the incidence of grade 3 or higher AEs and AEs leading to drug withdrawal in the olaparib group were lower than those in the standard treatment group. Based

on the results of the study[5], Olapanide was officially approved by the FDA in January 2018 to treat BRCA mutation and HER2 negative breast cancer after chemotherapy.

Talazoparib is a highly effective oral dual-mechanism PARPi with higher potency than olaparib and is currently the most effective PARP1/2 inhibitor in vitro[8]. In a phase I study, single drug treatment of tarazopanib in BRCA1/mutant patients with advanced breast cancer showed high single drug antitumor activity[8]. Further analysis of the study found that compared with single-drug (capecitabine, eribulin, gemcitabine, or vinorelbine) chemotherapy, talazoparib significantly prolonged mPFS, ORR, and 24-week clinical benefit rate (CBR = CR + partial response (PR) + stable disease (SD)) in HER2-negative locally advanced or metastatic (la/m) BC patients with BRCA mutations[9]. Patients with central nervous system metastases and other subgroups also benefited from PFS. Although there was no significant advantage in the overall population of the pantoprazole group, the time delay in clinical deterioration was up to 18 months, and the quality of life of patients was significantly improved. Based on this study, in October 2018,

Thalazopanil was approved by FDA for the treatment of HER2 negative breast cancer with BRCA mutation.

2.2 NTRK gene fusion inhibitor

The NTRK gene fusion involves NTRK1, NTRK2, and NTRK3, which encode the high-affinity nerve growth factor receptor, the human brain-derived neurotrophic factor/neurotrophin-3 growth factor receptor, and the neurotrophin-3 growth factor receptor, respectively. Approximately 1% of solid tumors exhibit somatic chromosomal rearrangements involving fusions of the NTRK gene, resulting in overexpression of the protein and its structural downstream activation, thereby promoting tumor growth. A study[10] found that all tumors with fusion in breast cancer were HER2 negative, and TN was more common.

Larotene is a highly effective and highly selective NTRK gene fusion inhibitor. The enrolled patients in the three single-arm multi-center studies all had unresectable or metastatic solid tumors, and no satisfactory alternative treatment options, or the tumors continued to deteriorate after treatment. The efficacy evaluation of larotene was based on 55 patients with NTRK gene fusion in 3 clinical trials[11]. This group of patients showed significant benefit after treatment with larotene, with an ORR of 75%, and the median duration of response (mDOR) and mPFS were not reached. The AEs were mainly grade 1, and the incidence of treatment-related grade 3 or 4 AEs was not more than 5%. 15% of patients reduced their dose due to AEs, but no patient discontinued the drug due to AEs. In November 2018, the FDA approved larotene for the treatment of NTRK gene fusion, and for patients with inoperable, metastatic, and previously treated PD or no alternative treatment for adult and pediatric solid tumors without known acquired drug resistance mutations[6].

Encorafenib is an active NTRK gene expression product with central nervous system activity, an effective inhibitor of anaplastic lymphoma kinase and ROS1[12]. The efficacy of different doses and regimens of encorafenib in 54 adult la/mNTRK-positive tumor patients was evaluated in 355 patients in 3 single-arm, multi-center ALKA, STARTRK-1, and STARTRK-2 clinical studies. The ORR was 57.4%, and all tumor types responded; mDOR, mPFS, and mOS were 10.4, 11.2, and 20.9 months, respectively[13]. Most treatment-related AEs were grade 1-2, and 27.3% of patients experienced drug reduction. Only a few patients discontinued treatment due to treatment-related AEs.

3. Application of immunocheckpoint inhibitor in the treatment of advanced triple negative breast cancer

3.1 PD-L1 antibody

At present, the antibodies targeting PD-L1 commonly used in clinical practice mainly include avelumab, atezolizumab, and durvalumab, all of which are humanized or fully human IgG1 antibodies.

Avelumab inhibits the binding of PD-L1 to PD-1 by binding to PD-L1, resulting in the inactivation of T lymphocytes. It was approved by the FDA for the first-line treatment of advanced renal cell carcinoma in combination with axitinib. At present, only one JAVELIN study has been reported in the clinical study of avelumab in the treatment of advanced TNBC[14-15]. This study applied avelumab to 168 patients with advanced breast cancer, and the results showed that the disease control rate was 28.0%, and the objective response rate was 4.8% (including 1 case of complete response and 7 cases of partial response); Among them, 58 patients with advanced TNBC treated with avelumab achieved higher objective response rates (8.6%) and disease control rates (31.0%), suggesting that patients with advanced TNBC may benefit more from immunotherapy.

Atzugumab can bind to PD-L1 and block its interaction with PD-1 and B7.1 receptors. It has been approved for the treatment of TNBC abroad. The IMpassion130 study is the first clinical trial to achieve positive results in the phase III clinical study of immunotherapy in advanced TNBC. The study showed that in patients with advanced TNBC, the objective response rate of atzugumab combined with albumin-bound paclitaxel treatment (atzugumab group) was 59%, the progression-free survival was 7.2 months, and the overall survival was 25 months; while the objective response rate of placebo combined with albumin-bound paclitaxel treatment (placebo group) was 43%, the progression-free survival was 5.5 months, and the overall survival was 18 months; Compared between the two groups, the objective response rate, progression-free survival, and overall survival in the atezolizumab group were significantly better than those in the placebo group. This study showed that the application of atezolizumab in the treatment of advanced TNBC patients can improve the efficacy, and the progression-free survival and overall survival of patients are also prolonged[16-17].

Dovecote is an anti-PD-L1 monoclonal antibody that prevents tumor immune escape by blocking the binding of PD-L1 to PD-1 and CD80. Dovecote was approved by the FDA for the treatment of unresectable, stage III non-small cell lung cancer patients who have not experienced disease progression after platinum-based chemotherapy and radiotherapy, as well as for combination therapy with etoposide and platinum (carboplatin or cisplatin) chemotherapy regimens, which can be used as first-line treatment for extensive stage small cell lung cancer. However, its clinical research in advanced TNBC has not yet been reported[18-21].

3.2 PD-1 antibody

PD-1 is mainly expressed in activated T lymphocytes and B lymphocytes. When T lymphocytes or B lymphocytes are overactivated, autoimmune diseases can be caused. PD-1 can inhibit cell overactivation. The tumor microenvironment can induce the high expression of PD-1 in infiltrating T lymphocytes, which binds to the PD-1 ligand of tumor cells, resulting in the continuous activation of the signaling pathway and inhibiting the function of T lymphocytes. Currently, the commonly used antibodies targeting PD-1 in clinical practice include Nivolumab, Pembrolizumab, Cemiplimab, Toripalimab, Sintilimab, and Camrelizumab, all of which are humanized or fully human immunoglobulin G4 (IgG4) antibodies.

At present, only pabolizumab has been studied in breast cancer. KEYNOTE-012 is a clinical

study of pembrolizumab in the treatment of PD-L1-positive advanced TNBC. In 27 evaluable patients, the objective response rate was 18.5%, including 1 complete response, 4 partial responses, and 7 disease progression. The median response time was 17.9 weeks (7.3-32.4 weeks), the disease control rate was 25.9%, the median survival time was 10.2 months, and the 1-year survival rate was 41.1%. KEYNOTE-086 treated advanced TNBC patients with pembrolizumab, and the results showed that the objective response rates in the ITT population and PD-L1-positive patients were 5.3% and 5.7%, respectively, and the disease control rates were 7.6% and 9.5%, respectively[18].

3.3 CTLA-4 blockers

Research shows that inhibitors targeting CTLA-4 can block the binding of CTLA-4 and B7, prevent the generation of T lymphocyte inhibitory signals, and enhance specific anti-tumor immune responses; by blocking CTLA-4 induction,

AKT signaling is activated, inhibiting the malignant proliferation of cells; Blocking CTLA-4 can also induce tumor cells to secrete increased levels of IL-2, affecting the immune microenvironment[21-22]. At present, only two humanized monoclonal antibodies of CTLA-4, trimezumab and epimab, have been reported in small samples of breast cancer.

4. Application of traditional Chinese medicine in the treatment of triple negative breast cancer

4.1 Microscopic Targeted Molecular Regulation of Traditional Chinese Medicine Treatment

Research has shown that regulating cell cycle and DNA damage sensing, DNA repair are widely used in clinical practice, providing the possibility of combined use with other chemoradiotherapy and targeted therapy[23]. After comparing the inhibitory effects of blank group, high, medium and low experimental groups of Yanghe Decoction on MDA-MB-231 cells, Li Kangle et al. found that the mechanism of inducing apoptosis is to block the cell cycle G2/M phase and activate the Egr1/p21 signaling pathway to achieve anticancer effects[24]. In order to identify the natural anticancer substances in the exocarp of Ginkgo biloba, Zhou Dayu used cytotoxicity tracking method to determine that the substance is 2-hydroxy-6-tridecanoylbenzoic acid, which is achieved by activating molecular targets of signaling pathways and inhibiting protein changes in epithelial mesenchyme[25]. In recent years, the conventional treatment of TNBC has reached a bottleneck, and exploring new mechanisms of action is of great significance for the treatment of TNBC. Qi Qi et al.[26] explained that oridonin has a significant inhibitory effect on the proliferation of MDAMB-231 cells from the perspective of reactive oxygen species. The mechanism may be related to the increase of intracellular reactive oxygen species and the downregulation of anti-apoptotic protein expression by oridonin, accompanied by the activation of caspase-3, which induces apoptosis in MDA-MB-231 cells. Further research is needed. Yes associated protein (YAP) plays a regulatory role in cell proliferation and apoptosis downstream of the Hippo pathway[27].

4.2 Application of traditional Chinese medicine treatment in advanced supportive treatment of triple negative breast cancer

Most patients with advanced TNBC have disease recurrence, ineffective chemotherapy, and weakened physical fitness after several treatments. The goal should be to slow down the disease process, alleviate clinical symptoms, and improve quality of life. Qiu Zhimin et al. used the combination of Yiqi Jiedu Formula and chemotherapy for advanced TNBC patients, and achieved significant therapeutic effects. Compared with the control group, the study group showed higher treatment efficiency, CD4+, CD4+/CD8+, and KPS scores, while the study group showed lower levels of carbohydrate antigen 125, carcinoembryonic antigen, and carbohydrate antigen 153 than

the control group. The combination of Yiqi Jiedu Formula and chemotherapy can not only enhance the efficacy of chemotherapy, but also alleviate the adverse reactions of chemotherapy, improve the patient's life, and is a practical and feasible program[28].

In summary, for patients with advanced TNBC, in addition to conventional chemotherapy regimens, targeted drugs, ICl, and ADC have begun to emerge, and the addition of traditional Chinese medicine can also play a good role. Whether it is first-line or multi-line treatment, there are suitable and effective drug options. The synergistic effect of combination therapy may further increase the clinical benefit of patients, but the current evidence is still insufficient and further exploration and analysis are needed. Precision therapy significantly prolongs the OS of patients with aTNBC, improves quality of life, and has controllable safety. Clinical treatment is increasingly becoming more precise. In the future, it is necessary to continue to search for new targets, develop new drugs, carry out new research, and also attach importance to the development and selection of individualized schemes, striving to maximize the therapeutic benefit of patients and minimize toxicity.

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