Research Progress of Immunotherapy and Its Application in Triple-negative Breast Cancer

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Abstract: For aggressive malignant tumors, many potential new treatment strategies have emerged in the field of immunotherapy. The most important breakthrough in the research field of triple-negative breast cancer is to clarify its immunophenotype and characteristics, and design new and targeted immunomodulatory targets for treatment. The most studied is the application of immune checkpoint inhibitors, which have achieved good results in the rescue treatment of advanced triple-negative breast cancer and the neoadjuvant treatment of early triple-negative breast cancer. This study reviews the research progress of cancer immunotherapy and its application in triple-negative breast cancer, especially the efficacy of immune checkpoint inhibitors combined with chemotherapy, radiotherapy and targeted therapy

1 Introduction

Breast cancer is the world's first cause of cancer death among women, and the incidence rate has increased significantly in recent years. Triple negative breast cancer (refers to a special type of breast cancer with negative expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2, accounting for 15% to 20% of all breast cancers. It lacks effective endocrine Treatment and targeted therapies, currently proven effective systemic treatments are mainly chemotherapy [1]. Patients often have recurrence or distant metastasis within a short period of time after chemotherapy, and the prognosis is poor. Therefore, explore effective methods that can be combined with chemotherapy drugs to improve Targeted drugs and molecular targets for curative effects have become a key clinical problem. Triple-negative breast cancer is the subtype of breast cancer that is most closely related to the tumor immune microenvironment. According to the results of gene sequencing, triple-negative breast cancer can be divided into different subtypes. One of the more common subtypes is the immunomodulatory subtype, which is closely related to tumor immune response and provides a breakthrough for finding effective chemotherapy and immune-targeted drugs for triple-negative breast cancer. In recent years, Immune checkpoint inhibitors have significant effects in various solid tumors, and they are also initially effective in triple-negative breast cancer. Combined with chemotherapy, radiotherapy and other targeted therapies can further improve the efficacy. This article will review the progress of cancer immunotherapy research And its application in triple-negative breast cancer, especially the clinical trial design of immune checkpoint inhibitors and their efficacy in combination with chemotherapy, radiotherapy and targeted therapy are reviewed and analysed [2].

2 Cancer Immunotherapy

2.1 Tumor Vaccine

Tumor vaccines use tumor cells, tumor antigens or other related biological components to stimulate the host to produce an effective anti-tumor immune response. Tumor vaccines include tumor cell vaccines, tumor antigen vaccines, dendritic cell vaccines, anti-idiotypic antibody vaccines, DNA vaccines and vaccines against tumor-related pathogens. Tumor cell vaccines have produced preliminary effects for the treatment of non-small cell lung cancer; tumor antigen vaccines are a synthetic antigen vaccine containing MUC1. A phase 111 clinical trial involving

1028 cases of metastatic breast cancer showed that the combination of Theratope and endocrine therapy can slow down disease progression and improve overall survival. DC vaccine has been clinically used in malignant melanoma, prostate cancer, lung cancer, and childhood malignant tumors. Trials and researches have achieved preliminary results; DNA vaccines have been used to treat malignant melanoma, breast cancer, prostate cancer, and cervical cancer [3].

2.2 T Cell-based Treatment

Secondary cell transport therapy is a transport therapy for individual patients' own immune cells (mainly T cells). The immune cells used in ACT include: lymphokine-activated killer cells, tumor infiltrating lymphocytes, cytokine-activated killer cells and macrophage-activated killer cells. CAPRI immune cell therapy is a new type of ACT. Due to its remarkable curative effect and wide practicability, its use exceeds other ACT methods. CAPRI immune cell therapy can destroy different types of tumor cells, including breast cancer, colon cancer and gastric cancer. Chimera antigen receptor (it is a natural T cell receptor without major histocompatibility complex restriction. Genetically modified CAR-T cells have been widely used in the treatment of various tumors, including lymphoma, malignant melanin Tumors, brain gliomas, etc., show effective targeting, greater toxicity, and durability of efficacy [4].

2.3 Therapeutic Antibodies

Therapeutic antibodies specifically target the cell differentiation antigen CD3/19/20/22/30/33/52, skin cell attachment molecules, cytotoxic T cell related antigens, PD-1 and PD-L 1, etc. Immune checkpoints are protective effectors of the human immune system. Tumor cells can overexpress immune checkpoint molecules to suppress the body's immune response, thereby evading immune surveillance. By blocking the transmission of immunosuppressive signaling pathways, checkpoint inhibitors can reverse the immunosuppressed tumor microenvironment and restore the killing function of cytotoxic T cells. Currently, the most researched are PD-1, PD-L1 and CTLA-4 inhibitors. Other immune checkpoints include lymphocyte activation gene 3, TIM-3, CD160, glycosyl phosphoinositide protein, T cell immunoglobulin, and mucin-3[5].

2.4 Cytokine Therapy

Cytokine therapy is to prevent and treat diseases by increasing the level of cytokines and promoting their biological functions. The CKs used for clinical treatment mainly include thymosin, IL-2, IFN, etc., and many of them are recombinant products. IL-2 is one of the most studied CKs. It promotes the proliferation of T cells through positive immune regulation. Induces the activation of NK, CTL and other immune effector cells, promotes B cell proliferation, differentiation and antibody formation. The combination of CK treatment and other treatments may become an important way of cancer immunotherapy.

3 Progress in Immunotherapy of Triple Negative Breast Cancer

3.1 Immune Checkpoint Inhibitors

Triple-negative breast cancer is one of the tumor types suitable for immunotherapy intervention due to its high genetic instability and mutation burden leading to the production of neoantigens, which can be easily recognized by the immune system. Triple-negative breast cancer has a higher level of tumor-infiltrating lymphocytes and PD-L 1 protein expression, suggesting the activity of its immune response [6]. Scoring by TILs count or immune markers found that patients with triple-negative breast cancer with high levels of TILs expression showed a better prognosis, even in patients with triple-negative breast cancer who did not receive chemotherapy. These results provide a strong theoretical basis for the use of immunotherapy in triple-negative breast cancer.

The JAVELIN Phase I clinical trial studied the efficacy of PD-L1 monoclonal antibody avelumab in different malignant tumors. Among them, there were 168 breast cancer patients. This clinical trial group is not a selective PD-L 1 positive expression patient. Shows that the overall remission rate is 4.8%. In the triple-negative breast cancer subgroup, when the PD-L 1 positive

expression threshold was selected as 10%, the remission rate of patients with positive expression reached 44.4%. In the KEYNOTE012 clinical trial (Phase IB), the PD-1 inhibitor Pembrolizumab was used as a single agent for triple-negative breast cancer at a dose of 10 mg/kg, administered once every two weeks. In this clinical trial, the positive threshold of PD-L 1 is defined as 1%, and 22C3 antibody is used for IHC detection. Among 111 cases of triple-negative breast cancer, 65 cases (58.6%) were PD-L 1 positive, the overall response rate was 18.5%, and 26% were stable disease. The other two phased clinical trials (KEYNOTE086) for patients with advanced triple-negative breast cancer with PD-L1 positive expression also achieved satisfactory remission rates. The plan adopted was a fixed dose of 200 mg, administered once every three weeks. (NCT02447003).

3.2 Immunotherapy Combined with Chemotherapy

Chemotherapy is the main treatment for triple-negative breast cancer adjuvant treatment and advanced salvage treatment. At present, the main chemotherapy regimen is the sequential or combined use of onion ring, cyclophosphamide and yew. However, studies have shown that scallion ring and oxaliplatin-based chemotherapy requires full immune activity to achieve the best therapeutic effect. For those patients with impaired immunity, this condition will become a hindrance. On the other hand, onion rings and oxaliplatin can induce tumor growth inhibition by inducing host immunogenic cell death and anti-tumor immune response. Interestingly, studies in the immune microenvironment of neoadjuvant chemotherapy for triple-negative breast cancer patients have shown that chemotherapy may serve as a key immunomodulatory effector, changing the immune environment from a "cold environment" (low TIL expression) to a "cold environment" (low TIL expression). Thermal environment" (high TIL expression) [7].

Most patients newly diagnosed with early triple-negative breast cancer received neoadjuvant chemotherapy. Studies have shown that patients with residual disease after neoadjuvant chemotherapy have a worse prognosis, which may be related to the secondary expansion of host immunosuppressive cells, the reduction of immune effectors, and the formation of chemotherapy-resistant clones. Therefore, it is reasonable to further strengthen the treatment. Choices include single-agent immunomodulatory drugs or a combination of immunomodulatory drugs and chemotherapy [8]. The SWOG1418/BR006 study was conducted for patients with residual surgery after neoadjuvant chemotherapy. After the operation, the PD-1 inhibitor pembrolizumab was continued to be administered every three weeks for 52 weeks. Keynote522 (NCT03036488) Phase III clinical study aimed at stage II-III early triple-negative breast cancer, comparing the efficacy difference between Pembrolizumab and neoadjuvant chemotherapy combined with neoadjuvant chemotherapy alone, in which Pembrolizumab needs to be used sequentially for 1 year. The results It showed that the pCR of the combination group and the control group were 64.8% and 51.2%, respectively, and the difference was statistically significant ($P<0.001$). Another phase IB clinical study, Keynote 173, which evaluated the safety and effectiveness of Pembrolizumab and neoadjuvant chemotherapy, also showed that its toxicity is controllable. The dose of Pembrolizumab is 200 mg and the overall pCR reaches 60%. Further exploratory analysis suggests, PCR and PD-L1 positive expression are positively correlated with stromal tumor infiltrating lymphocytes [9]

In the rescue treatment stage of advanced triple-negative breast cancer, there are also some clinical trials for the combination of chemotherapy and immunotherapy. The recently published Impassion130 study showed that the PD-L1 inhibitor Atezolizumab combined with paclitaxel alone in patients with metastatic and locally advanced triple-negative breast cancer showed a significant benefit of mPFS compared to chemotherapy alone, which directly led to the FDA's approval of PD-L 1 inhibitors are used in the treatment of such patients, and the FDA defines PD-L 1 positive as those whose expression is greater than 1% detected by VEN-TANA PD-L1 (SP142). These data suggest that the combination of immunotherapy and chemotherapy will greatly improve the prognosis of patients with advanced triple-negative breast cancer. At the same time, these studies also indicate that it is particularly important for us to screen effective biomarkers for people who benefit from the combination of immunotherapy and chemotherapy.

3.3 Immunotherapy and Targeted Therapy

Although triple-negative breast cancer lacks clear targets, such as HER2, estrogen receptor, and progesterone receptor, after neoadjuvant chemotherapy, 90% of triple-negative breast cancers have mutations in signaling pathways. The target is currently in the clinical research phase. These targets include: PARP inhibitors, PI3K inhibitors, histone dephenolase inhibitors, TP53/MYC inhibitors and TGFp inhibitors. Clinical trials for these new targets alone or in combination with immunotherapy are also being widely carried out.

3.4 Immunotherapy and Radiotherapy

A phased clinical study evaluating the PD-1 inhibitor Pembrolizumab combined with radiotherapy for advanced triple-negative breast cancer showed that the overall response rate of the primary endpoint was 17.6%, and no grade 4 serious adverse reactions occurred. Aguilera et al. added radiotherapy-sensitive triple-negative breast cancer cells to the tumors of radiotherapy-insensitive mice and received radiotherapy together. They found that M1 subtype macrophages and DC cells that inhibit tumor progression increased, and M2 macrophages that promote tumor progression decreased. , To form an immune-promoting tumor microenvironment, thereby improving the efficacy of immunotherapy. Both in vivo and in vitro studies indicate that radiotherapy can promote triple-negative breast cancer cells to release damage-related model proteins, promote the recruitment of neutrophils and monocytes, the activation of endothelial cells, and the differentiation and maturation of antigen presenting cells, which are conducive to immune response. Environment, improve the synergistic effect of radiotherapy and immunotherapy [10].

3.5 Secondary Cellular Immunotherapy

In a clinical study of 90 cases of surgical removal of triple-negative breast cancer, 45 cases received chemotherapy or radiotherapy, and the remaining 45 cases received cytokine-induced killer cell injection therapy combined with chemotherapy or radiotherapy. The study showed that the subgroup receiving CIK combination therapy showed better DFS and OS. Multivariate analysis showed that CIK adjuvant therapy is an effective independent prognostic indicator for triple-negative breast cancer. The study suggests that chemotherapy-assisted CIK therapy has significant advantages in preventing the recurrence of triple-negative breast cancer and prolonging overall survival.

4 Conclusions

Immune checkpoint inhibitors and secondary cellular immunotherapy are the two major achievements of cancer immunotherapy. By overcoming tumor-induced immunosuppression, immune-mediated tumor clearance can play a leading role. However, some patients will still develop resistance to existing immunotherapy, leading to immune escape, making the overall efficacy of immunotherapy poor. In triple-negative breast cancer, the combined use of chemotherapy, radiotherapy and new targeted therapies with existing immunotherapy methods, especially immune checkpoint inhibitors, greatly improves the efficacy of immunotherapy. This suggests that for triple-negative breast cancer patients who have no special effective endocrine therapy and targeted therapy, seeking an effective combination of immune checkpoint inhibitors and chemotherapy or other targeted immune therapies may improve their long-term survival Effective means.

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