Breast Cancer: Targets and Therapy

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REVIEW

Recent Advances in Immunotherapy for Breast Cancer: A Review

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Abstract: Breast cancer is one of the most common malignant tumors in women in the world, and its incidence is increasing year by year, which seriously threatens the physical and mental health of women. Triple negative breast cancer (TNBC) is a special molecular type of breast cancer in which estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 are negative. Compared with other molecular types of breast cancer, triple-negative breast cancer (TNBC) has high aggressiveness and metastasis, high recurrence rate, lack of effective therapeutic targets, and usually poor clinical treatment effect. Chemotherapy was the main therapeutic means used in the past. With the advent of the immune era, immunotherapy has made a lot of progress in the treatment of triple-negative breast cancer (TNBC), bringing new therapeutic hope for the treatment of triple-negative breast cancer. This review combines the results of cutting-edge medical research, mainly summarizes the research progress of immunotherapy, and summarizes the main treatment methods of triple-negative breast cancer (TNBC) immunotherapy, including immune checkpoint inhibitors, tumor vaccines, adoptive immunotherapy and the application of traditional Chinese and western medicine. It provides a new idea for the treatment of triple negative breast cancer (TNBC).

Keywords: breast cancer, triple negative breast cancer, immunotherapy, immune checkpoint inhibitors, tumor vaccine, adoptive immunotherapy

Introduction

In today's world, according to the International Agency for Research on Cancer (IARC) survey data show that there are about 19.3 million new cancer patients in the world every year, and about 10 million patients die, of which breast cancer has surpassed lung cancer to become the most common cancer in the world, breast cancer has become the highest incidence of cancer in the world, and the incidence is also rising year by year.[1] Triple-negative breast cancer (TNBC) refers to breast cancer with negative expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2, which has clinical characteristics such as strong invasion, easy early recurrence and poor prognosis, accounting for about 15–20% of clinical cases, and is difficult to benefit from endocrine therapy and HER-2 targeted therapy.[2,3] In the past, breast cancer was generally regarded as a "cold tumor" with low immunogenicity, and it was difficult to benefit from immunotherapy. However, with the development of modern medicine, there are more and more treatment methods for breast cancer. As an emerging treatment method, immunotherapy has achieved certain effects in the treatment of breast cancer and has been paid more and more attention. Especially in triple negative breast cancer (TNBC), TNBC is considered to have the most immune prototype of breast cancer subtype, the number of tumor infiltrating lymphocytes (TILs), the expression of programmed death receptor-ligand (PD-L1) and tumor mutation load (TMB) are higher than other subtypes of breast cancer. This suggests that the tumor immune microenvironment (TME) of triple-negative breast cancer (TNBC) has strong immune activity, and its treatment may have great potential to transform from immune "cold tumor" to "hot tumor".[4,5] Among them, the most representative immunotherapy means are the application of immune checkpoint inhibitors, the representative applications are PD-L1/PD-1 and CTLA-4 inhibitors

Received: 12 June 2024
Accepted: 19 August 2024
Published: 27 August 2024

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respectively. However, the effect of immune checkpoint inhibitors alone is not ideal in the treatment of breast cancer, and the combined application of immunotherapy with traditional treatment schemes can benefit from it. And can achieve the effect of 1+1 > 2, especially in the treatment of triple negative breast cancer (TNBC) the benefit rate is relatively high. At the same time, other immunotherapies such as tumor vaccine, adoptive immunotherapy, combined Chinese and Western medicine therapy also provide new ideas and means for the immunotherapy of triple negative breast cancer (TNBC). With the development of immunotherapy research, combined with the data and results of multiple clinical trials, it can be found that immunotherapy will receive more and more attention in the treatment of TNBC.

Breast Cancer Molecular Typing

Breast cancer is a highly heterogeneous disease, and the response and prognosis of different individuals to clinical treatment vary greatly. Different molecular types of breast cancer have different clinical treatment plans. According to the research results, the analysis of molecular typing of breast cancer based on gene expression level has become the key basis for clinical treatment of breast cancer.[6] Estrogen receptor (ER), Progesterone receptor (ER), PR), Human epidermal growth factor receptor-2 (HER-2) and Ki-67 were expressed in different ways to type breast cancer.[7] Currently recognized molecular types of breast cancer are Luminal A type, Luminal B type, HER-2 overexpression type, and triple negative type. Luminal A means ER and/or PR positive, HER2 negative, Ki-67 index ≤14%, Luminal B can be divided into two types, one is ER and/or PR positive, HER2 negative, Ki-67 index > 14%; The other type is ER and (or) PR positive, HER2 positive, that is, triple positive type, TNBC type is ER and (or)PR negative, HER2 negative three are negative expression.[8]

Different molecular types have different therapeutic characteristics and clinical characteristics. Luminal A is the most common molecular subtype of breast cancer, accounting for about 70% of breast cancer, with the highest clinical cure rate and the best prognosis. It is more common in early stage breast cancer, and the risk of recurrence is lower. Adjuvant chemotherapy was given to high-risk groups, and the higher the ER/PR expression was, the better the therapeutic effect was. The clinical representative drugs included luteinizing hormone releasing hormone (LHRH), namely ovarian function inhibitors Goserrelin, leprerelin, etc. Aromatase inhibitor tamoxifen and so on. Luminal B is for HER2-negative type, and the Ki-67 index is greater than 14%, and patients are treated with endocrine therapy, and most patients are treated with chemotherapy.[9] Luminal B type is targeted at HER2-positive type, and Ki-67, triple positive breast cancer under any state, is prone to axillary lymph node and distant metastasis, accounting for about 6.2% of breast cancer, and more metastases occur in more than two sites, and the greater the number of metastases, the worse the prognosis. Clinical treatment is usually endocrine therapy plus chemotherapy combined with trastuzumab.[10] HER-2 overexpression type, ie, ER/PR negative type and HER2-positive type, accounts for about 15%-20% of breast cancer, which is highly invasive and has a poor prognosis. Due to low ER/PR expression, endocrine therapy is not effective, and HER2-targeted drugs combined with chemotherapy are often used in clinical treatment, and the commonly used drugs are purple-based combined trastuzumab therapy[11,12](Table 1).

Triple-negative breast cancer (TNBC) refers to that ER, PR and HER2 are all negative, accounting for about 15–20% of breast cancer. TNBC usually occurs in premenopausal women under 40 years old, with short survival period and 12–18 months overall survival (OS), poor clinical cure rate, poor prognosis, low differentiation, high invasibility, prone to local and distant metastasis, high recurrence rate, and high mortality. Because the expressions of all three are negative, the clinical effect of endocrine therapy and targeted therapy is not good, and the clinical treatment is mainly chemotherapy.[13] According to current studies, among the molecular subtypes of breast cancer, TNBC has a unique immune microenvironment with more tumor-infiltrating lymphocytes and tumor-associated macrophages, so TNBC has great hope and prospect for immunotherapy in the future.[14]

TNBC can be divided into six subtypes: Basal cell-like 1 (BL1), basal cell-like 2 (BL2), interstitial M, interstitial stem (MSL), immunomodulatory (IM), and surface androgen receptor expression type (LAR).[15] Immunomodulatory triple-negative breast cancer is sensitive to immunotherapy, accounting for about 24% of TNBC cases, and has a better prognosis compared with other subtypes, which also means that this subtype will have a more ideal effect of immunotherapy.[16]

Table 1 Breast Cancer's Molecular Classification

Molecular Typing	Clinical Proportion	Molecular Expression	Peculiarity	Means of Treatment	Representative Drug
LuminalA	70%	ER, PR(+); Ki-67 is less than 14%; HER2(-)	The clinical cure rate is high, the prognosis is best, it is more common in early breast cancer, and the risk of compound is low.	Endocrine therapy (hormone therapy) is often used alone, with adjuvant chemotherapy for high-risk groups.	Leuprorelin, Goserrelin; Tamoxifen; Anastrozole, letrozole; CDK inhibitors, etc
LuminalB	6.2%	ER, PR(+); Ki-67 is higher than 14%; HER2(-)		Endocrine (hormone therapy), but some are treated with chemotherapy.	Endocrine therapy combined with trastuzumab targeted drug therapy Endocrine combined application targeted therapy.
		ER, PR(+); Ki-67 in any state; HER2(+)	Axillary lymph node metastasis is easy to occur, and more metastasis occurs in two or more sites, and the more metastasis, the worse the prognosis.		
HER2	15%-20%	ER, PR(-); HER2(+)	It is highly invasive and has a poor prognosis. Due to the low expression of ER and PR, the effect of endocrine therapy is poor.	Her2-targeted drugs combined with chemotherapy.	Trastuzumab; The combination of paclitaxel and trastuzumab is commonly used.
TNBC	15%	ER, PR(-); HER2(-)	It usually occurs in premenopausal women under 40 years old, with a short survival period and an overall survival period of 12–18 months. The clinical cure rate is poor, the prognosis is poor, the differentiation is low, the invasiveness is high, the local metastasis is easy to occur, and the recurrence rate is high. Due to the low expression of the three, the endocrine and targeted therapy effects are poor.	Chemotherapy; immunotherapy	Paclitaxel; Pabolizumab; Altezumab.

TNBC Immunotherapy Benefits

When it comes to the development of breast cancer, the tumor immune microenvironment and the number of lymphocytes that infiltrate the tumor have both historically been regarded as low immunogenic tumors. After conducting extensive research, we discovered that removing several molecular types of breast cancer allowed us to detect a larger level of tumor immune infiltration in TNBC. Tumor-infiltrating lymphocytes, PD-L1, and tumor mutation load (TMB) can all be expressed at increased levels. Because of this, TNBC is thought to be the most immunogenic subtype of breast cancer, and immunotherapy works better against it than it does against other molecular subtypes of the disease.[17]

Our defense mechanism

The innate and adaptive immune systems make up the human immune system. The human body's organs that create immune cells include the lymph nodes, spleen, thymus, and bones. The human immune system is destroyed when germs and other toxins enter the body. Adaptive immune cells, on the other hand, start to function when viruses infiltrate the human body deeper. Certain pathogens can reach B cells, which can then use endocytosis to break down the antigen and present on the cell

surface to function as antigen-presenting cells (APCs), which stimulate helper T cells.[18] At this point, certain pathogens can also be consumed by other antigen-presenting cells, like dendritic cells, which break down the antigens within the cells and create complexes that are then processed and presented on the cell surface. T helper cell receptors identify the complexes when antigen-presenting cells come into contact with them, relaying information to T helper cells. After combining with antigen-stimulated B cells, the activated helper T cells activate B cells. Helper T cells proliferate, become activated, and release cytokines. The two signals cause B cells to proliferate and differentiate, with the majority of them differentiating into plasma cells as a result of the cytokines helper T cells secrete. The production and secretion of a vast quantity of antibodies, which bind to pathogens and bodily fluids during entire body circulation, is the role of plasma cells. Antibodies can bind to infections and prevent them from multiplying. Antibodies and antigens combine to generate precipitates, which other immune cells phagocytose and disintegrate.[19] The T cell, which is derived from bone and develops into various receptors before migrating to the thymus to mature, is a particularly significant immune system cell. Unlike B cells, the T cell membrane expresses the T cell receptor (TCR), a special antigen-binding molecule that is linked to antigens that recognize membrane proteins known as histocompatibility complex (MHC) molecules.[20] Gu-Trantien's group discovered that T cells constituted approximately 75% of the major role in lymphocytes infiltrating breast cancer tumors, with B cells accounting for about 20%, monocytes for about 10%, and NK cells for the smallest percentage or approximately 5%.[21,22]

Tumor immune evasion

The human body's immune system is a dynamic developmental process that involves immune monitoring, tumor immunoediting, and the identification and removal of new cancers. The three stages of this process are the escape period, the equilibrium period, and the clearance period.[23] Tumor-related signals will activate the body's immune system throughout the early stages of a tumor. At this point, tumor cells will be destroyed by the immune system of the human body, and innate immune cells such as neutrophils, NK cells, dendritic cells, and macrophages will also kill the tumor cells. Tumor-specific T cells move to the surface of tumor cells to either kill tumor cells or produce drug-resistant clonal mutations when B cells and other differentiated antigen-presenting cells (APCs) activate tumor-specific CD8+ and CD4+T cells. This process occurs while the tumor continues to grow. The immune system is at a standstill with the tumor cells that have not been eradicated during the equilibrium stage. At this point, the tumor cells undergo immunological remodeling. The immune system eliminates the highly immunogenic tumor cells, while the less immunogenic tumor cells will mutate and persist. Currently, tumors can develop a range of defense mechanisms against immune surveillance, or they can develop immunosuppressive properties of their own. Examples of these defense mechanisms include the destruction of antigen-presenting mechanisms, the enhancement of negative immune regulatory pathways, the recruitment of tumor-promoting immune cells, etc. At this point, the tumor enters the clinical stage after overcoming the immune system's inhibition of it.[24]

The Tumor Microenvironment (TME) of TNBC

The immune microenvironment of breast cancer lesions, that is, the local internal environment composed of tumor cells, immune cells and tumor-related fibroblasts, which enter into the breast cancer tissue and secrete cytokines, plays an important regulatory role in the growth, proliferation and metastasis of cancerous cells.[25] Tumors resist anti-tumor drugs through multiple mechanisms, and studies have confirmed that the tumor microenvironment plays a central role in this process. Tumor immune microenvironment (TME) is a dynamic microenvironment composed of a large number of immune cells, Tumor-associated macrophages (TAMs), tumor-infiltrating lymphocytes (TILs), antigenic presenting cells (APC), tumor-associated fibroblasts (CAF), mesenchymal cells, endothelial cells, extracellular matrix (EMC), etc., have different proportions, and infiltration levels with different proportions are called immune cell infiltration.[26] When normal cells transform into tumor cells, tumor mutation load occurs, and tumor cells will produce corresponding secretions to attract immune cells and fibroblasts to gradually inhibit their tumor killing function. At the same time, it should not be ignored that endothelial cells are generated in the tumor immune microenvironment, which will provide nutrients to the tumor and further promote the growth of the tumor.[27] The development of tumor is closely related to related cancer cells and the surrounding environment. When tumor cells interact with immune cells, they can both anti-tumor and promote tumor, resulting in a two-way effect, which plays a decisive role in the development trend of tumor and affects the progression and metastasis of tumor. Breast cancer has long been considered a low immunogenic tumor with a low

mutation load due to limited T cell infiltration. However, with the continuous progress of research, it is found that triple-negative breast cancer (TNBC) can show more tumor infiltrating lymphocytes, and the tumor mutation load rate increases, which provides a new idea for immunotherapy.[28] TNBC has a higher proportion of tumor infiltrating immunity than other breast cancer subtypes. TILs is composed of different cells, such as lymphocytes, macrophages, plasma cells, monocytes, dendritic cells, memory T cells, etc. It exists in the tumor stroma or in the tumor cells and is a heterogeneous lymphocyte population dominated by lymphocytes. It plays a role in immune response and regulation in the immune mechanism of tumors, killing tumor cells and reducing the distant and multiple metastasis of tumors. Observing high immune cell infiltration in tumors is considered to be an adaptive mechanism of the immune system, which can prevent the growth and metastasis of tumors.[29] Breast cancer tumor-infiltrating lymphocytes (TILs) have been shown to be prognostic and potentially predictive of breast cancer, especially in TNBC.[30] This is because TNBC can exhibit higher levels of TILs and have a higher capacity for tumor mutation load (TMD).[31] The higher the TILs level, the higher the overall survival in TNBC, and the combination chemotherapy can improve the immune response of the tumor. There are also high levels of tumor-associated macrophages (TAM) and regulatory T cells (Tregs) in the immune microenvironment of TNBC, which can produce immunosuppression on the body, but can also be transformed under certain circumstances. Tumor-associated macrophages (Tams) are expressed in the tumor microenvironment. As a monocyte, macrophages can differentiate into M1 proinflammatory macrophages and M2 anti-inflammatory macrophages. In the tumor immune microenvironment, tumor-associated macrophages were mostly immunosuppressive M2 and anti-inflammatory, which played an immunosuppressive role. M1 and M2 macrophages will release the corresponding cytokines, M1 releases IL-6, TNF-α, INF-γ and other pro-inflammatory cytokines, M2 releases IL-10 anti-inflammatory, that is, immunosuppressive cytokines, both of which will cause the polarization of macrophages.[32] By gradually transforming M2 in the micro-environment into M1 type through reprogramming and reducing the immunosuppression of M2 type, tumor growth can be further inhibited. One subtype of helper T cells, Th1, will release INF-γ, INF-γ and other cytokines to promote the polarization of M1 cells, and the expression of Arg-1 and MHC-II will be promoted when M1 is polarized. The release of TNF-α, INF-γ, NO, etc. promotes the proliferation and activation of cytotoxic T lymphocytes (CTL) and NK cells to exert anti-tumor activity. In the pro-inflammatory environment, these cytokines can promote cellular immunity and form an anti-cancer environment. Another subtype of helper T cells, Th2, will release cytokines such as IL-4 and IL-13 to promote the polarization of M2 cells. When M2 is polarized, cytokines such as IL-10 and TGF-β will be released to play an immunosuppressive role, inhibit the expression of NK cells, promote the expression of PD-L1, and block the infiltration of effector T cells. Exert immunosuppression and promote the further development of tumor. At the same time, M2 will release TGFβ, IL-4, IL-10 and other cytokines, inhibit the activity of cytotoxic T lymphocytes, up-regulate the differentiation and expression of regulatory T cells (Treg), perform immunosuppression, and form a cancer-promoting environment[33] (Figure 1).

In summary, compared with other subtypes of breast cancer, we can find that there is a higher level of immune expression in the immune microenvironment of triple-negative breast cancer, which suggests that there is great potential and hope for the application of immunotherapy for triple-negative breast cancer.

Illustrated description: 1. There are a large number of immune cells in the immune microenvironment of triple-negative breast cancer, including antigen-presenting cells, dendritic cells, tumor-associated macrophages, effector T cells, and myeloid suppressor cells. 2. All kinds of immune cells are stimulated by the corresponding cytokines to differentiate into immunosuppressive cells and anti-tumor cells to promote and kill breast cancer cells respectively; 3. A variety of immune cells interact in the tumor immune microenvironment, forming a dynamic microenvironment to regulate the generation, development and inhibition of breast cancer.

Immunotherapy for Breast Cancer That is Triple-Negative

The goal of tumor immunotherapy is to eradicate tumor cells in the body by stimulating and adjusting the host's natural defense system to produce immunomodulators, antibodies, or immune cells that have a better anti-tumor effect. Immunotherapy can be classified into three categories based on its mechanism: adoptive immunotherapy (cells, antibodies), active immunotherapy (tumor vaccines, immune genes, etc)., and non-specific immunomodulators.

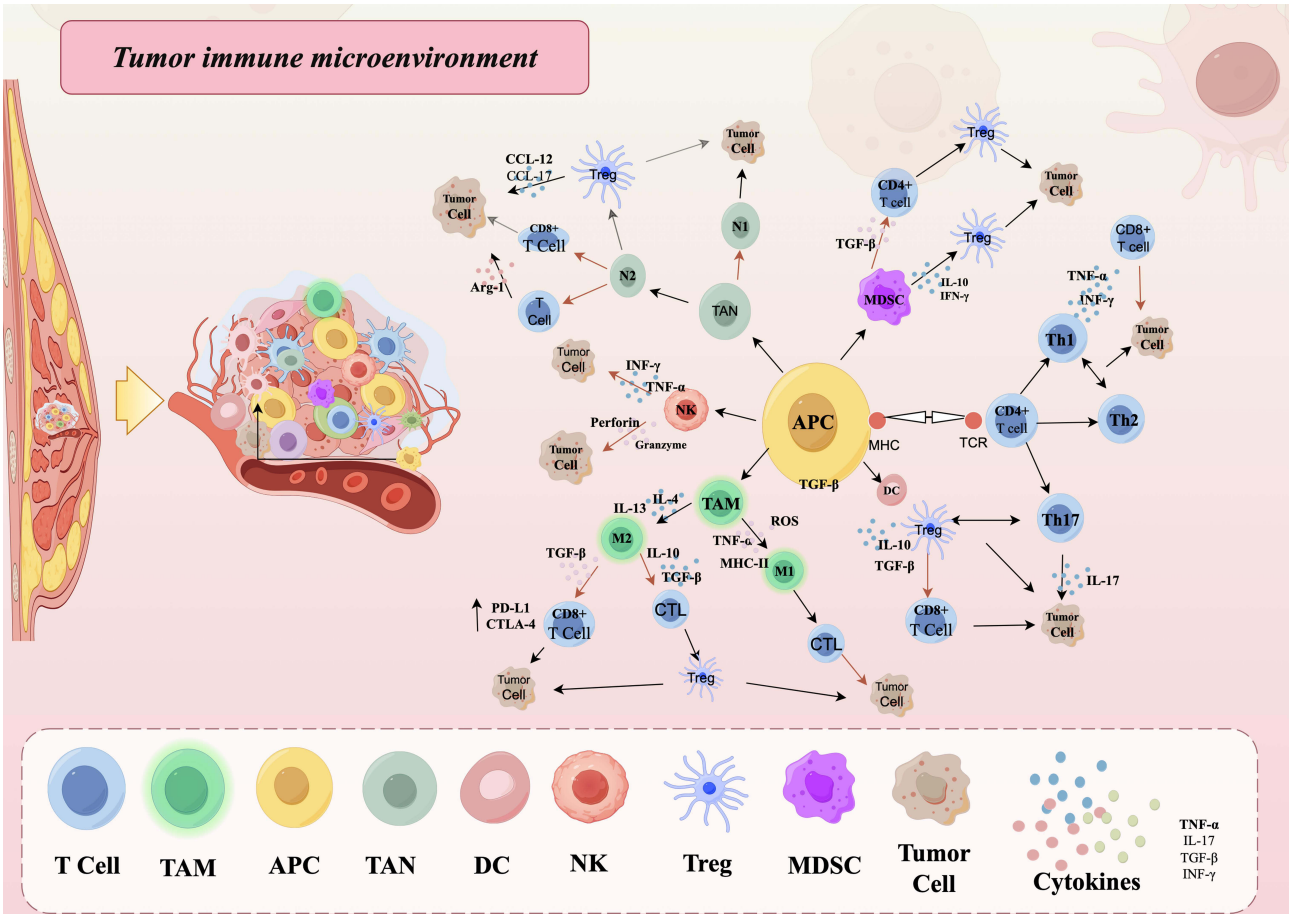

Figure 1 Tumor immune microenvironment By Figdraw (ID:TYWYUdd4bd).

General immune modulators

Non-specific immunomodulators have two main types of anti-cancer mechanisms: those that stimulate effector cells to treat tumors, like alpha interferon, IL-2, imiquimod, and the BCG vaccine; and those that block PD-1 and PD-L1, like anti-CTLA-4 monoclonal antibody, which acts by inhibiting immunonegative regulatory cells or molecules. In contemporary clinical practice, both pathways are the most researched targets for immunological checkpoint inhibitors and can suppress CD8+ and CD4+T cell responses. Immune checkpoint inhibitors (ICIs) are the most effective immunotherapy drugs for triple-negative breast cancer. They work by blocking immunosuppressive receptors, which enhance the cytotoxicity and proliferation of tumor-infiltrating lymphocytes and reactivate the killing effect of T cells on tumors.

PD-L1/PD-1 inhibitors

PD-L1/PD-1 blocks The foundation for breast cancer survival is the immunosuppressive microenvironment, which is mediated by the PD-L1/PD-1 signaling pathway. It also plays a significant role in the emergence, progression, and avoidance of immune surveillance of breast cancer. At the moment, decision-making is guided by the biomarker PD-L1 expression in malignancies.[34]

While PD-L1 is expressed on tumor cells, activated T cells, and macrophages in the tumor microenvironment, PD-1 is a significant immunosuppressive protein that is typically present on the surface of T, B, NK, and other immune cells. Tumor-associated macrophages (TAMs) also exhibit high levels of PD-L1 expression, with a longer half-life than that of tumor cells.[35] M1 and M2 types of TAMs can be distinguished based on the various activation signals they receive. M2 types of tumor-related macrophages can contribute to the formation, growth, and distant metastasis of tumors within the tumor immune microenvironment by secreting growth factors and cytokines. They can also release immune cell

suppressor factors to prevent T cells from killing tumors.[36] Inhibiting T cells is PD-L1. Tumor growth is stimulated by cytotoxic T lymphocytes' efficient inhibition of tumor cells and the weakening of immunoregulatory T cells' activity by binding to the programmed death receptor (PD-1) on T cell surfaces.[37]

Therefore, by blocking the route between PD-1 and PD-L1, monoclonal antibodies can limit their binding, improve immune response against tumors, boost T cell function, and restore immunological activity in the tumor microenvironment. Since TNBC has the highest level of PD-L1 expression, PD-L1 inhibitors are the most popular and effective treatment for TNBC. According to research, TNBC performed PD-L1 immunohistochemistry and discovered that PD-L1 was expressed by triple-negative breast cancer. This finding supports the possibility that PD-L1 could be a target for triple-negative breast cancer immunotherapy, which has significant research implications.[38,39]

The KEYNOTE series examined the use of palolimumab in solid tumors, including stomach, non-small cell lung, and breast cancers. Experiments on pembrolizumab in breast cancer, including KEYNOTE-012, 086, 355, 522, and others, have also proven that pembrolizumab in combination with chemotherapy can produce optimal outcomes in a range of TNBC stages. Palivizumab inhibitors on their own can lower the tumor mutation burden in patients with advanced triple-negative breast cancer stage Ib, according to the KEYNOTE-012 experiment. They also have good anti-tumor effectiveness and safety.[40] KEYNOTE-086, the study demonstrated that a single pembrolizumab injection provides good therapeutic benefits for advanced triple-negative breast cancer.[41,42] KEYNOTE-119 was carried out in Phase II and III trials of neoadjuvant therapy for metastatic triple-negative breast cancer from September 2018 to January 2022. Patients with metastatic triple-negative breast cancer did not see improvements in OS, PFS, or ORR with palozumab alone, according to the results of a Phase III trial combining chemotherapy with the medication.[43] In patients with early-stage, high-risk neoadjuvant therapy for stage Ib non-metastatic triple-negative breast cancer, KEYNOTE-173 was conducted from February 18, 2016, to February 28, 2017. The study found that higher pre-treatment PD-L1 combined positive scores with chemotherapy combined with pembrolizumab and sTIL before and during treatment were significantly associated with higher rates of partial response (PCR) and that 12-month event-free survival and overall survival ranged from 80% to 100% in each group.[44] KEYNOTE-355 uses either placebo or pembrolizumab in combination with chemotherapy to treat triple-negative breast cancer that has spread locally, was previously untreated, or had relapsed. The findings demonstrated a substantial increase in overall survival in triple-negative breast tumors with OD-L1 expression and CPS of more than 10 when pembrolizumab with chemotherapy was administered.[45,46] The Phase III study results for KEYNOTE-522, a trial involving patients with stage II and III triple-negative breast cancers who had not received prior treatment, indicated that palivizumab plus chemotherapy had a superior clinical therapeutic effect for early-stage patients with triple-negative breast cancers compared to placebo plus chemotherapy. The trial was conducted from March 2017 to September 2018.[47–49] Bolozab plus neoadjuvant chemotherapy increased the PCR rate of high-risk early-stage breast cancer patients, as demonstrated by the I-SPY experiment.[50] In conclusion, several KEYNOTE series findings have demonstrated the enormous promise of PD-L1 inhibitors in the treatment of triple-negative breast cancer, offering fresh approaches and resources for the disease's therapeutic management (Table 2).

The Impassion series is the first to investigate attezumab's use in triple-negative breast cancer by studying PD-L1/PD-1 inhibitors. Patients with triple-negative breast cancer that was locally progressed, metastatic, or incurable were treated with atezolizumab and albumin-bound paclitaxel in the Impassion130 study. The results of the investigation showed that patients with PD-L1 positive tumors who received atezolizumab plus albumin-bound paclitaxel had a considerable improvement in progression-free survival.The PFS results matched those from the Phase III study of KEYNOTE-355 with chemotherapy for triple-negative breast cancer.[51–53] To assess alemtuzumab as the first-line treatment for unresectable, locally advanced, metastatic triple-negative breast cancer, the Impassion131 trial is a Phase III study that combines paclitaxel with or without alemtuzumab. The study's findings demonstrated that paclitaxel, either alone or in combination with atlizumab, did not increase the investigators' PFS.[54] The PCR of patients with PD-L1-negative PD-L1-positive patients treated with atrezizumab combined with paclitaxel or anthracycline-based chemotherapy showed improvement compared with placebo-combined chemotherapy, according to the Impassion031 trial, a Phase III trial of atrezizumab in combination with neoadjuvant chemotherapy for early-stage triple-negative breast cancer. Treating patients with early-stage triple-negative breast cancer with atezumab and chemotherapy shows remarkable promise.[55,56] PFS in patients who have relapsed less than 12 months after chemotherapy for early-stage triple-negative breast cancer has an advantage when administered with

Table 2 Data from the PD-L1/PD-1 Inhibitors Keynote Series

Clinical trials	Molecular typing	Clinical drug use	Antitumor activity and safety	Effect	Conclusion
KEYNOTE-012[40]	Late TNBC Ib	Pabolizumab alone	With an acceptable safety profile, the incidence of 3–5 and treatment-related adverse events was 15.6%, and the tumor burden decreased in 37.5% of cases. Its anticancer activity is good.	Effective mitigation	ORR18.5%; CR:3.7%; PR:14.8%; SD:25.9%
KEYNOTE-086[41,42]	Late TNBC Ib	Pabolizumab alone	With a grade 3 treatment-related adverse event rate of 9.5%, it had an acceptable safety profile. No. 4 and unfavorable outcomes. Its anticancer activity is good.	Effective mitigation	ORR:21.4%; DCR:23.8%
KEYNOTE-119[43]	Metastatic TNBC III	Chemotherapy VS Pabolizumab alone	26.9% of treatment-unrelated events of grade 3 or higher occurred.	Pabolizumab alone had no remission compared with chemotherapy alone	OS without remission
KEYNOTE-355[45,46]	Late TNBC	Pabolizumab plus chemotherapy vs placebo plus chemotherapy	Associated class 345 adverse events Pabolizul combined chemotherapy group: 68.1%. Placebo combined with chemotherapy: 66.9%. Mortality rate of pabolizumab combined with chemotherapy: 0.4%; Placebo combined chemotherapy mortality: 0%.	Effective mitigation	Pabolizumab Anti-combination chemotherapy OS: 23 months, 58.3%; CDR: 70.5%. Placebo combined with chemotherapy OS: 16.1 months, 44.78%; CDR: 81.6%.
KEYNOTE-522[47–49]	Early TNBC	Pabolizumab plus chemotherapy vs placebo plus chemotherapy	Mortality was 0.4% and 78% of patients receiving pabolizumab in addition to chemotherapy experienced grade 3 or higher adverse effects.Mortality was 3% and 73% of adverse events were grade 3 or above.	Effective mitigation Effective mitigation	Pabolizumab group: PCR: 64.8%; Placebo group: PCR:51.2%.
I-SPY2[50]	Early TNBC	Pabolizumab in combination with neoadjuvant chemotherapy	Pabolizumab combined with chemotherapy had a higher incident-free rate.	Effective mitigation	Pabolizumab combined with neoadjuvant chemotherapy: PCR:60%. Control group: PCR: 22%.

natalizumab, according to the Impassion132 trial, a Phase III clinical trial of ocrelizumab for the treatment of early-stage triple-negative breast cancer patients with disease progression within 12 months of chemotherapy, that is, early relapse less than 12 months after chemotherapy.[57,58] Patients with operable stage II and III triple-negative breast cancer were enrolled in the Impassion030 trial, which used either chemotherapy alone or natalizumab in combination with chemotherapy. The outcomes demonstrated that patients with triple-negative breast cancer might achieve successful remission. In conclusion, several findings from the Impassion series have demonstrated the significant promise of PD-L1 inhibitors in the management of triple-negative breast cancer, offering a fresh approach and new tools for the disease's treatment clinical trials ent (Table 3).

CTLA-4 inhibitors

Transmembrane protein CTLA-4, commonly referred to as CD152, is the second member of the B7-CD28 family. It is a chemical that co-inhibits T cells, causing T cells to be negatively regulated. Moreover, monocytes, B cells, dendritic cells, granulocytes, and other cells can express CTLA-4 concurrently.Research has revealed that compared to healthy individuals,

Table 3 Impassion Series Research Data on PD-L1/PD-1 Inhibitors

Clinical trials	Molecular typing	Clinical drug use	Effect	Conclusion
Impassion130[51–53]	An unresectable locally advanced or metastatic TNBC assay	Altezumab combined with albumin-paclitaxel VS placebo combined with chemotherapy	Both are effective in relieving	Pabolizumab plus chemotherapy ITT group VS placebo plus chemotherapy group: PFS:7.2 vs 5.5(month); PD-L1 positive group: 7.5VS5.0(month); PFS:21.3VS11.6 (month); PD-L1 positive group 6.0VS5.7(month);
Impassion131[54]	Unresectable locally advanced or metastatic TNBC	Atizumab combined with chemotherapy vs placebo combined with chemotherapy	Combined application did not improve	Atizumab combined chemotherapy vs placebo combined chemotherapy PFS:6 vs 5.7 months. PD-L1 positive atizumab combined with chemotherapy showed no difference in OS compared with chemotherapy group.
Impassion031[55,56]	Early TNBC	Atizumab combined with chemotherapy vs placebo combined with chemotherapy	Both are effective in relieving	Atezumab combined chemotherapy VS placebo combined chemotherapy: ITT: CR:57.6% vs 41.1%; PD-L1 positive CR: 69% vs 49%.
Impassion132[57,58]	TNBC recurred within 12 months after early chemotherapy	Atizumab combined with chemotherapy vs placebo combined with chemotherapy	Both are effective in relieving	ORR, OS and PFE of Altezumab combined with chemotherapy were superior in both groups
Impassion030	Operable TNBC	Atizumab combined with chemotherapy vs.chemotherapy	Both are effective in relieving	It is feasible.

breast cancer patients had far higher serum levels of CTLA-4. The B7 family's CD80 and CD86 are normally expressed by antigen-presenting cells (APCs), while T cells express CD28. T-cell activation requires the presence of at least one immune system stimulation.[59] Antigen-presenting cells (APC) have CD80 and CD86 ligands that CD28 attaches to as a co-stimulator on T cells, enabling T cells to destroy tumor cells. The cytoplasmic vesicles contain CTLA-4. Under the influence of T cell interaction molecules, CTLA-4 is transported to the cell membrane upon T cell activation.[60] To attach to the CD80/86 ligand on antigen-presenting cells (APC), CTLA-4 will now compete with CD28 co-stimulatory factors. As a result, CTLA-4 will prevent T cells from being activated by CD28 co-stimulatory factors and lessen the ability of T cells to eradicate malignancies. Furthermore, antigen-presenting cells (APC) CD80/86 will be ingested by CTLA-4 from the outside of the cell inside the cell, reducing both CD80/86 and the ligand that CD28 may bind to. This reduces the ability of T cells to eradicate malignancies.[61] Because of this, anti-CTLA-4 inhibitors work by, among other things, preventing CTLA-4 from attaching to T cells that have CD80/86 and obstructing the negative immunological response that results from it. This allows CD28 to work in concert with CD80/86 to fulfill its intended function. T cells appear to be overactivated at this point, which may increase their ability to kill tumor cells. increases the immune system's cytotoxic reaction.[62] Conversely, anti-CTLA-4 drugs can enhance CD80/86 expression, prevent antigen-presenting cells (APC) from endocytosing CD80/86 ligand, improve CD28's ability to bind to CD80/86, and stimulate T cells to eradicate malignancies. Clinical research has demonstrated that using antibodies to block CTLA-4 can trigger a powerful immune response that eliminates tumor cells. CTLA-4 inhibitors, on the other hand, are more frequently employed in the treatment of malignant melanoma and have demonstrated good clinical curative outcomes. As a result, it is possible to continue developing techniques for researching the use of CTLA-4 inhibitors in breast cancer[63,64] (Figure 2).

In conclusion, the application of immune checkpoint inhibitors (ICIs) to block the PD-L1/PD-1 and CTLA-4 signaling pathways to restore the anti-tumor immune response is a new method for the treatment of triple-negative breast cancer. The present status and challenges of immune checkpoint inhibitors (ICIs) in the treatment of early-stage

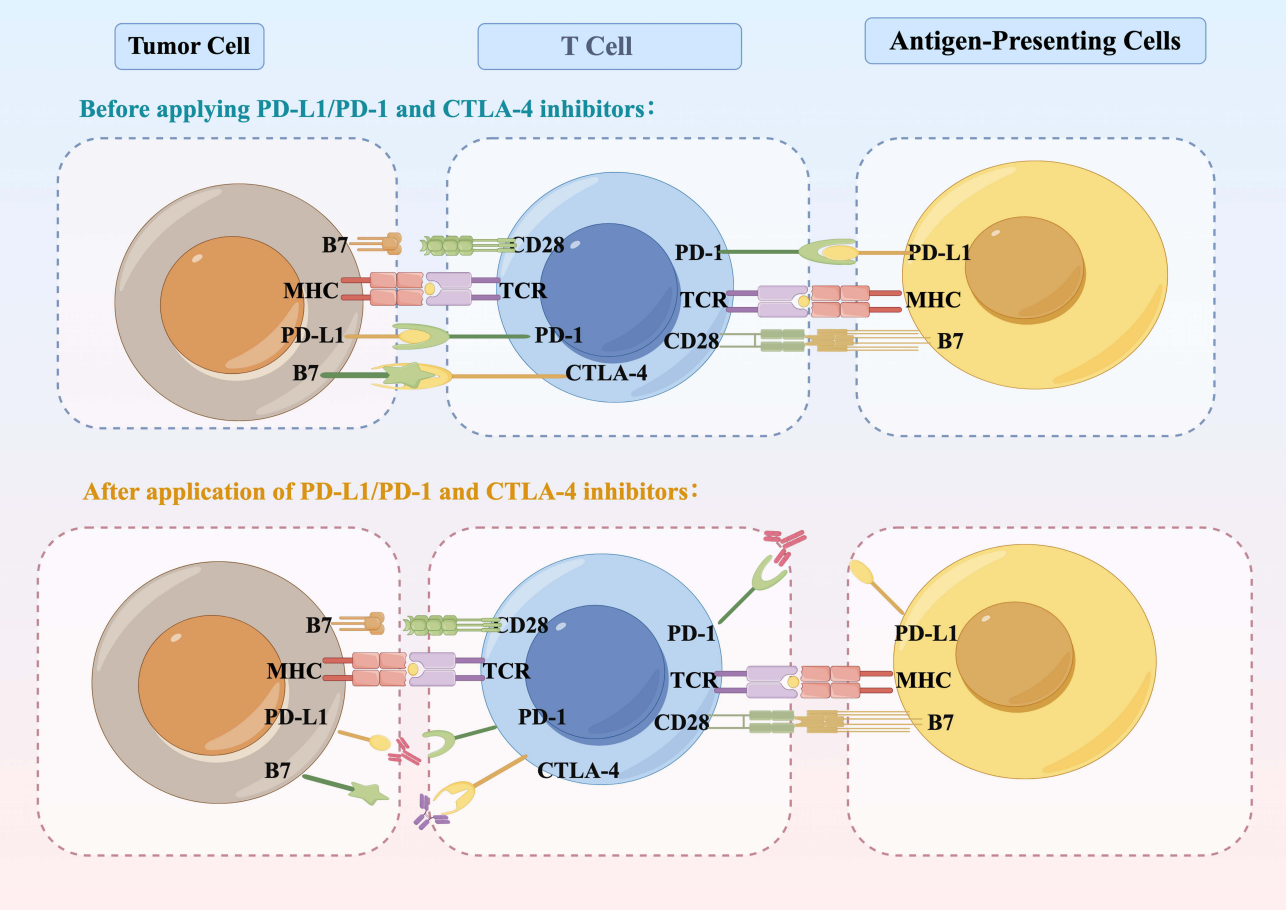

Figure 2 Mechanism of immune checkpoint inhibitors. By Figdraw (ID: OARPWbd2bb).

and late-stage triple-negative breast cancer are summarized in this paper. We found that ICIS combined with other treatments such as chemotherapy can show a good application prospect for patients with early-stage and late-stage triple-negative breast cancer. However, there are still some problems that need to be solved, such as the in-depth research and clinical investment of CTLA-4 inhibitor detection molecules, and the optimization of PD-L1 detection methods. But overall, the application of immune checkpoint inhibitors offers a very promising immunotherapy approach for the treatment of triple-negative breast cancer.

Illustrated description:1. PD-L1, MHC and B7 were expressed on the surface of tumor cells, PD-1, TCR, CD28 and CTLA-4 were expressed on the surface of T cell, and PD-L1, MHC and B7 were expressed on the surface of antigen-presenting cells. 2. When PD-L1 is combined with PD-1 and B7 with CTLA-4, immunosuppression will occur, further promoting tumor growth. 3. After the application of PD-L1/PD-1 and CTLA-4 inhibitors, the binding of PD-L1 with PD-1 and B7 with CTLA-4 is blocked, and the anti-tumor activity is restored.

Tumor Vaccine

One of the most important breakthroughs in the history of human medicine is the development of vaccinations. The use of penicillin by Coley et al in the early 20th century is where vaccinations first appeared. It is crucial for the management and avoidance of many illnesses, particularly infectious ones. To destroy tumors, tumor-specific immune responses are elicited by tumor vaccines using tumor cell cleavage products, tumor-specific antigens, tumor-associated antigens, tumor peptides, or anti-idiotype antibodies.[65] Enhance the immunogenicity of tumor-associated antigens. Overcome immunosuppression brought on by tumor products. Mediates specific anti-tumor active immunity. Stimulates specific immune attacks against tumor cells. Improves the immune system's capacity to recognize tumor antigens.[66] Tumor vaccines can create immune

memory of production time, which is a benefit, but their anti-tumor effect is long-lasting and sluggish, making them more appropriate for patients with modest tumor mutation loads. Tumor vaccines are better suited for usage in patients with high tumor mutation loads after surgery, radiation therapy, and chemotherapy to lower the patients' mutation loads.

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Tumor-specific antigens and tumor-associated antigens are two categories of tumor antigens. Vaccines against related tumor antigens can activate the immune system, specifically kill cancer cells, extend the body's immunological memory, and lower the incidence of cancer recurrence.Tumor vaccines can be classified into various categories according to the kind and source of antigens. These categories include genetically engineered cell vaccines, polypeptide vaccinations, viral vector vaccines, dendritic vaccines, molecular targeted vaccines, and protein or peptide vaccines.[68]

Cellular Vaccines

The strongest antigen-presenting cells in the human body are called dendritic cells. Dendritic cells are found throughout cancerous tissues. They are expressed in the tumor microenvironment, identify antigens unique to tumors, and subsequently deliver these antigens to host lymphocytes to activate the body's immune system and destroy cancerous cells. Nonetheless, dendritic cells' ability to destroy immune cells is reduced and their activity is impeded in the tumor microenvironment to allow the tumor to grow larger. Unactivated or immature dendritic cells can be isolated from the peripheral blood of tumor patients, directly transfected with TAA or TAAS encoding vectors to DC, and activated when specific cytokines are used to stimulate them. Dendritic cells (DCS) can present exogenous and endogenous antigens to CD8 and CD4T cells, respectively. Activated dendritic cells can now be delivered to the patient, presenting TAAS to CD8 and CD4 to trigger a potent immune response.[69] Therefore, to boost the immune system's ability to eradicate tumor cells, dendritic cells were created in vitro and then given to or immunized to individuals suffering from triple-negative breast cancer. The RUNX2-dendritic cell gene vaccine has been shown in clinical experiments to activate certain immune cells that kill triple-negative breast cancer.[70]

Particularly in DC, which is generally benign and non-toxic, cellular vaccines have a tremendous deal of potential for immune activation, excellent tolerance, and safety. But it also has drawbacks, such as expensive production costs, a protracted cycle, and a challenging procedure. As a result, to produce immunostimulated dendritic cells and prevent immunosuppression in the tumor immune microenvironment, the settings must be optimized. Clinically speaking, it still takes a while to get over.

Polypeptide Vaccines

The linked peptides in the vaccination attach to the Class I and Class II human leukocyte antigens (HLA) on the imperial cells (APC) to create the polypeptide-HLA complex when the vaccine is injected into the body. The polypeptide-HLA complex is recognized by CD8 cells in the T cell family, which then generate cytotoxic lymphocytes (CTLS). Lastly, perforin, grease, and cytokines are released by cytotoxic lymphocytes when they identify tumor cells that express the antigen and kill those cells.[71] GP-2 vaccine, After surgery, the GP-2 vaccine can be given as a supportive treatment for early-stage breast cancer. Patients with high levels of HER-2 expression can benefit from the GP2 vaccination, which is a fragment of HER-2 and comprises a 9 amino acid transmembrane protein. To activate antigen-presenting cells and further encourage CD8T cells and cytotoxic T lymphocytes to recognize tumors and eliminate HER-2 cancer cells, it is injected into the body along with GM-CSF (immune adjuvant). Clinical research has demonstrated that patients with the GP-2 vaccine have T cells that can detect ovarian and breast cancers with high expression of HER-2, excite T cells continually, and use the body's powerful immune system to stop the disease from returning.[72,73] AE37 vaccine, Patients with low HER-2 expression are better suited for the AE37 vaccine, a novel HER-2-focused vaccination based on the AE36 hybrid peptide, which is produced from the intracellular portion of the HER2 protein and the core component of the MHC-II invariant chain. The co-administration of GM-CSF immunological adjuvant, which targets CD8 cells and stimulates CD4 activity to destroy tumor cells, is also necessary for the use of the AE37 vaccination. Clinical

investigations have demonstrated that the most stable vaccination for patients with invisible lymph nodes and no clinical recurrence is AE37.[74,75] Neu-Vax vaccine, The Neu-Vax vaccine is appropriate for patients with low to moderate HER2 expression. It comprises an immune-stimulating oligopeptide generated from the HER2 protein, also known as E75, which is relatively highly expressed in breast cancer. The GM-CSF immune adjuvant must be applied in conjunction with this vaccination. By stimulating and activating CD8, CTL, and CD8 memory cells to E75 and MHC-I epitopes, the vaccine can recognize and eliminate HER2 primary and metastatic cancer cells through cell lysis. Activated specific CTL can also bind to HLA molecules on antigenic king cells. After inducing the growth of peptide T lymphocytes, eliminate malignant cells.[76] Despite their ease of synthesis, relative safety, and reduced susceptibility to side effects, peptide vaccines have certain drawbacks. For instance, APC can co-stimulate T cells more effectively, but for it to function as a vaccine, immunological adjuvants are required. However, these vaccines only target specific epitopes, and when tumor-associated antigens change, malignancies can evade the immune system.[77]

Protein Vaccine

Treatment for HER2-type breast cancer is successful when using the peptide vaccination mentioned above. Higher benefits can also be obtained from the triple-negative breast cancer protein vaccination in terms of its therapeutic effect. The α-lactalbumin vaccine, MIAC targeting vaccine, and Globe-H glycoprotein targeting vaccine are the representative vaccinations.[78] Alpha-lactalbumin vaccine, α-lactalbumin expression is comparatively elevated in breast cancer, particularly in triple-negative breast cancer, where it is significantly greater than in other forms of the disease. Based on this, α-lactalbumin has undergone extensive clinical research. Triple-negative breast cancer patients have high levels of alpha-lactalbumin, a protein that is essential to breast milk and is absent in non-lactating women. Triple-negative breast cancer may be eradicated by stimulating the body's potent immune system through the use of alpha-lactalbumin as a novel target.[79] Targeting MIAC vaccine, By using the CTL route, malignancies can produce immunological escape during the aforementioned immunoediting dynamic process. As cancer cells develop, they remove the MICH protein from the cell membrane's surface, creating escape. Clinical research has revealed that individuals with triple-negative breast cancer who have a prolonged survival time have higher antibody levels, which may inhibit the proteolytic release of MHIC. Clinical research has demonstrated that, when proteolysis is the target, this vaccination can generate the MHIV proteolytic antibody, stop proteolysis, and prevent the body's immune system from destroying the cancer cells by preventing the MHIC protein from falling off their surface.[80] Developing vaccines targeting Globo-H glycoprotein, We discovered that Globo-H is expressed on the surface of some triple-negative breast cancer stem cells as well as on the cancer cells themselves, as compared to certain normal cells in the body. This suggests that increasing the globe-H glycoprotein vaccine can raise the survival rate of individuals with triple-negative breast cancer.[81] A protein vaccination can prevent certain HLA epitope restrictions, greatly increase T cell activation, kill and destroy cancer cells, and enhance and repair the body's immune system. Its drawbacks include challenging synthesis, a lack of safety, and structural stability in therapeutic settings.[82]

VirUs-Based Tumor Vaccines

Oncolytic virus vaccine, The virus-based tumor vaccination can stimulate both the i nnate and adaptive immune systems to produce a durable and potent immune response. A pro-inflammatory milieu can be induced by the inherent immunogenicity and oncolytic activity of viruses, and oncolytic viruses in particular can elicit distinct anti-tumor immune responses. Oncolytic virus therapy can stimulate an immune response specific to tumor antigens while eliminating tumor cells. Once tumor cells are infected, oncolytic viruses can kill tumors directly, release cytokines and reactive oxygen species, and promote dendritic cell maturation and CD8+ and CD4+T cell activity. TAA is released when lysing tumor cells. It can have a role in the body's immune system and enhance the particular immune response to tumor antigens.[83] Research has demonstrated that the optimal outcome for treating patients with triple-negative breast cancer involves combining VTEC with neoadjuvant chemotherapy; the two-year recurrence-free efficiency is approximately 89%. Clinical results indicate that the combination of oncolytic virus plus CTLA4 and PD-L1 inhibitors has a considerably better therapeutic impact than oncolytic virus alone. Additionally, there is an increase in the number of lymphocytes that infiltrate tumors. For triple-negative breast cancer, the oncolytic virus can therefore be used as an adjuvant treatment in conjunction with other therapies[84] (Table 4).

Table 4 Tumor Vaccine

Vaccine type	Specific classification	Advantage	Shortcoming
Cellular vaccine	A dendritic vaccine	Strong safety, excellent tolerance, non-toxic, and safe. It has a potent immune-stimulating impact and is capable of activating T cells provide defense of the immune system against a range of antigens.	The production cycle is lengthy, expensive, and labor-intensive, adaptability is constrained, and a strong immune system is needed.
Polypeptide vaccine	GP-2 vaccine; AE37 vaccine; The Neu-Vax vaccine;	Simple synthesis, comparatively good safety, and poor tolerance for adverse effects. Minimizing non-specific reactions is achieved by precisely targeting certain antigens.	To function as a vaccine, it requires the assistance of immunological adjuvants and is not effective on its own. Vaccines only work on specific epitopes, and mutations in tumor-associated antigens lead to immune escape from malignancies. Individuals respond to immunizations in very different ways.
Protein vaccine	Alpha-lactalbumin vaccine; Targeted MIAC vaccine; Targeting Globe-H glycoprotein vaccine	It can bypass some HLA epitope limitations, greatly increase T cell activity, kill and destroy cancer cells, and strengthen and enhance the immune system.	In practical practice, synthesis difficulty, safety, and structural stability are still lacking.
Viral vaccine	Oncolytic virus vaccine	Strong safety, excellent tolerance, non-toxic, and safe. It has a potent immune-stimulating impact and is capable of activating T cells provide defense of the immune system against a range of antigens.	The production cycle is lengthy, expensive, and labor-intensive, adaptability is constrained, and a strong immune system is needed.

To sum up, the various breast cancer vaccines discussed above have certain advantages and disadvantages in clinical research and application. Although there are many promising results, compared with other immunotherapies, they do not show significant effects and more clinical benefits. The ultimate goal of our application of tumor vaccine therapy is to use the inherent inductivity and specificity of the host immune system to produce more durable and memory-strong activity, produce faster and more powerful immunity, kill breast cancer cells, and eventually cure breast cancer, and breast cancer vaccine will make a strong sprint to achieve this goal.

Adoptive Immunotherapy

Cellular adoptive immunotherapy and monoclonal antibody treatment directed against tumor antigens are the two primary forms of adoptive immunotherapy. Adoptive immunotherapy is more useful for patients with advanced tumors who have established immunological tolerance and are incapable of generating an immune response since it does not require the body to produce an initial immune response, unlike active immunotherapy. In cellular adoptive immunotherapy, immune effector cells that have been separated from autologous or allogeneic cells are activated in vitro and then returned to the host to eradicate malignancies. Research has demonstrated that potent cells can penetrate tumor cells and stimulate the surrounding tissue to eradicate the tumor and carry out their anti-tumor function.[85] The process of inducing and activating immune effector cells in vitro to generate a sufficient number of cytotoxic cells that can recognize tumor antigens is known as cellular adoptive immunotherapy.[86] Its benefit is that, when reinjected into the patient, it can have potent anti-tumor actions and is not vulnerable to immunosuppression by the host. Nonetheless, it is impossible to overlook the current issues, which include the intricacy of the in vitro production process, the difficulty of quality control, the high cost, and the limited scope of individual variances.[87]

The tumor releases particular factors that lead to tumor invasion and metastasis, which in turn attracts immunosuppressive cells to the tumor microenvironment. Immune cells in the microenvironment, such as NK cells and cytotoxic T lymphocytes, can identify tumor cells in the circulation and kill them by releasing grease and perforin, which causes the tumor cells to undergo apoptosis. Simultaneously, the release of TNF-α and IFN-γ encourages the growth of

additional immune cells and draws in more immune cells to destroy tumor cells.[88] Cytotoxic T lymphocytes: they can identify both their own MHC molecules and tumor antigen complexes; they also possess potent killing and tumor-specificity abilities, and they can stimulate antigen-presenting cells to present themselves more effectively, which helps break the immune tolerance state and improves T cell recognition. Antigen-presenting cells must be activated to perform their role.[89] Chimeric antibody receptor (CAR) T/NK cells: T/NK cells and the tumor-associated antigen are genetically recombined, and then T/NK cells are transfected to create CAR-T/CAR/NK cells. These cells can effectively kill antigen-loaded cells and have a high affinity for particular tumor antigens. Its function is immunological memory-based, it can be stored in the body for a long period, and MHC does not limit it. Recent research has demonstrated that while it is ineffective against solid tumors, it is useful in treating blood disorders. Triple-negative breast cancer may benefit from the use of tumor-associated macrophages in the tumor immune milieu since they can invade solid tumors and eradicate tumor cells. Additionally, these macrophages may last a prolonged period within the tumor immune microenvironment.[90]

Due to the limited T cell infiltration, breast cancer has always been considered as a low immunogenic tumor and a low mutation load. However, with the continuous progress of research, it has been found that triple-negative breast cancer can show more tumor infiltrating cells and the tumor mutation load rate increases. The research on adoptive immunotherapy provides a new idea for immunotherapy.

Combination of Traditional Chinese and Western Medicine

Research on how Chinese medicine and chemotherapy together can affect immune regulation and mechanism in triple-negative breast cancer patients, as well as how Chinese medicine and immunotherapy interact with one another. There is a unique treatment approach for immunotherapy used to treat triple-negative breast cancer, which is mixed in Western and Chinese medicine. Different molecular forms of breast cancer are treated by Western medicine, however, there are issues with side effects, including the immune system and chemotherapeutic side effects. Different molecular types of breast cancer can also effectively reduce toxicity and relieve symptoms when treated with Chinese medicine, given the numerous adverse effects associated with Western medicine treatment.[91]

In traditional Chinese medicine, breast cancer is classified as “milk rock”, “milk stone carbuncle”, and other terms, such as “flower milk”.[92] There are three stages of triple-negative breast cancer: early, middle, and late. Numerous studies have demonstrated that immunotherapy in conjunction with other forms of treatment has a more favorable outcome than immune checkpoint inhibitors by themselves. Given the various adverse effects of immunotherapy in conjunction with preoperative and postoperative surgery, as well as chemotherapy and radiotherapy, there are two main approaches to using immunotherapy in the treatment of triple-negative breast cancer.[93]

Breast cancer types can be classified as follows: spleen deficiency spittoon coagulation, Chong Ren disorder, phlegm toxicity stagnation, liver-Qi stagnation, liver-kidney Yin deficiency, liver-Qi stagnation blood stasis, etc. Xiaoyao Powder, Chaihu Shugan Powder, Liujunzi Decoction, Erchen Decoction, Taohong Siwu Decoction, Bazhen Decoction, Huangqi Jiadu Decoction, Shenling Baizhu Powder, etc. are among the frequently used prescriptions.[94] Among the Chinese patent medications are the following: Pingxiao capsule, Kangfuxin solution, compound Danshen dripping pill for peripheral neuropathy, Diyusheng Bai tablet, Qizhu Shengbai Tablet, and Shengxue Bao for myelosuppression, Lizhong pill for gastrointestinal side effects, and Dahuoluo pill for cardiotoxicity.[95,96] It is important to note that several research has shown that Xihuang Pill is very beneficial in the treatment of breast cancer.[97,98] TCM acupuncture can be utilized to treat cancer pain in patients with triple-negative breast cancer by boosting lymphatic reflux, releasing lymphatic fluid, unblocking lymphatic vessels, and lowering tumor load. The majority of acupoints that are clinically chosen are Sanyinjiao, Upper Juxu, Lower Juxu, and Zusanli.[99,100] Soaking with traditional Chinese medicine and other techniques can help to decrease peripheral neuropathy by increasing blood circulation.[101] You can treat sleeplessness using god gate, spleen, heart, and ear acupuncture, among other forms of prolonged stimulation.[102] Before or after surgery, edema can be relieved and upper limb circulation improved with the use of acupressure and fumigation, two traditional Chinese medical techniques.[103] Ear acupuncture or acupoint treatment in conjunction with acupuncture can be used to treat vomiting symptoms.[104,105] By using the aforementioned therapeutic approaches, patients’ unfavorable symptoms can be lessened, their immunological burden can be further decreased, and immunotherapy can function more effectively (Figure 3).

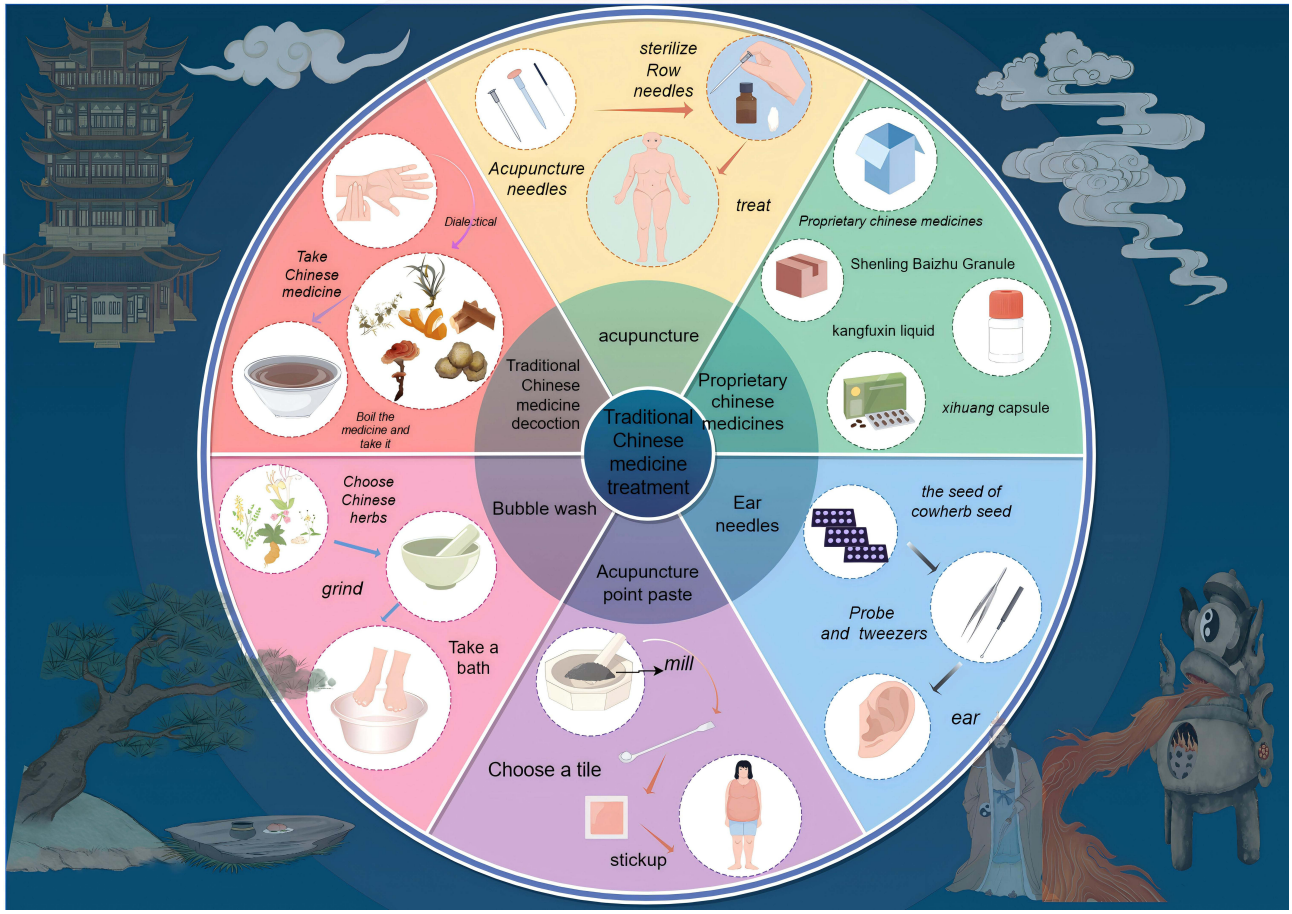

Figure 3 Chinese medicine's treatment of triple-negative breast cancer By Figdraw (ID: OWOWO99988).

Illustrated description: 1. Combined treatment of Chinese and Western medicine can further improve the body's immunity and restore the patient's anti-tumor ability. 2. After looking, smelling, asking, cutting, prescription decocting herbal medicine oral; Acupuncture treatment after pulse diagnosis; After grinding the Chinese medicine powder successfully, as for the boiling water, the Chinese medicine soaking; The Chinese medicine is ground into powder, as for dressing paste, paste on the acupuncture points; Take the ear needle, select the acupuncture point in the ear of the patient, paste the interval massage; Oral Chinese patent medicine. 3. Through a variety of TCM internal and external administration methods, combined with immunotherapy, to further improve patients' immunity, enhance anti-tumor activity.

When Western and traditional Chinese medicine are combined to treat triple-negative breast cancer, it has been discovered that traditional Chinese medicine can help patients with the disease by either up or down-regulating certain immune pathways, one of which is the crucial NF-κB signaling pathway.[98] Nuclear transcription factor NF-κB is a critical component of the cell that regulates inflammation, apoptosis, and immunity. It also contributes to the development of diseases and produces cytokines that exacerbate chronic inflammation and tumors. NF-κB can be activated through a variety of downstream pathways, and tumor immune infiltrating cells are one way that this can happen. It has a dual effect; while it helps numerous cells, including T and NK cells, fight cancer, it also keeps Treg and bone marrow-derived suppressor cells (MDSC) active, which has a pro-tumor effect.[106] It has been demonstrated that TNBC possesses overexpressed and highly activated NF-κB.[107] Several studies using MDA-MB-231 cell tumor mice have demonstrated that icariin can effectively induce oxidation-induced apoptosis of TNBC cells through the SIRT6/NF-κB signaling pathway, inhibit metastasis, regulate the immunosuppressive microenvironment, and promote the recovery of TNBC patients.[108] The overactivation of the AKT pathway in MDA-MB-468 cell studies is a characteristic shared by many cancer species, including TNBC, and is a crucial route influencing the proliferation and survival of cancer cells. Fritiline saponins can prevent ATK from being phosphorylated, indicating that

the ATK/ NF-κB signaling pathway is active.[109] It has been demonstrated that diosgenin may bind to the NF-Kb P65 subunit, indicating that diosgenin can block the NF-κB signaling pathway in TNBC cells. By preventing this system from being activated, diosgenin may encourage TNBC cell apoptosis and prevent tumor cell migration.[110] When paclitaxel and ginsenosides are combined, the NF-κB pathway increases the susceptibility of cancer cells to paclitaxel, induces apoptosis in TNBC cells, and can partially overcome the paclitaxel resistance.As a result, we can conclude that traditional Chinese medicine inhibits TNBC by controlling the body's immunological response via the NF-κB signaling pathway.[111]

To sum up, the immunotherapy of breast cancer has made great progress in recent years. The basic mechanism of TCM therapy is to regulate the immune microenvironment of breast cancer. The "Yin and Yang" of traditional Chinese medicine is closely related to the tumor immune microenvironment. In recent years, with the in-depth development and application of various operations such as single TCM, compound TCM, TCM acupuncture, and ear acupuncture, we found that the combined application of traditional Chinese and Western medicine can further restore the anti-tumor activity of immune cells by regulating the signaling pathway of tumor immune microenvironment and various targets. Therefore, we look forward to the combination of more TCM treatment and immunotherapy, and the combination of clinical and basic research, so as to better exert the regulation of TCM on the immune microenvironment of triple-negative breast cancer and inhibit the further development of tumors.

Adverse Reactions Associated with Immunotherapy

Based on the above summary and analysis of modern immune clinical treatment methods for triple-negative breast cancer, the treatment prospect is increasingly clear, but the accompanying adverse immune reactions of different degrees are also major problems that need to be solved. Immunotherapy is to use the patient's own immune system to destroy tumor cells, but when the immune system mistakenly targets the healthy cells of the patient's own immune system, it will lead to the imbalance of the patient's own immune tolerance, accumulated adverse reactions of different degrees, called immune-related adverse reactions (irAEs).[112]

Mainly manifested in the organs, often in skin toxicity, cataract, maculopapules, pruritus, concentrated in the limbs and trunk; Gastrointestinal diarrhea, vomiting, nausea; Alanine aminotransferase, aspartate aminotransferase and total bilirubin increased in liver. Endocrine manifestations of thyroid dysfunction, diabetes, pituitaritis; Immune-related pneumonia presents dyspnea, pneumonia and non-cavity; It is relatively rare in cardiac toxicity and side effects, the clinical manifestations are cardiac arrest, myocarditis, heart failure; Neurotoxicity with clinical manifestations of headache, dizziness, meningitis and myasthenia gravis; Renal toxicity, clinical presentation of renal failure.[113,114.]

It has a time rule and is accompanied by reversibility, and the occurrence rule mostly appears in 1–6 months after medication. The occurrence time of different adverse reactions is also accompanied by rules, and the occurrence time is from 3 short to late, respectively, liver toxicity, lung toxicity, endocrine toxicity, skin toxicity, and endocrine recovery time is relatively long.[115]

Adverse immune reactions to tumor vaccines are relatively weak, but some clinical studies have found that there are non-specific memory cells when tumor vaccines are treated, which will replace previously existing beneficial memory cells, have a disastrous effect on antibodies, and lead to further development of tumors.[116]

The purpose of the combined treatment of Chinese and Western medicine is to restore the immune ability of the body, but after the application of immune checkpoint inhibitors, there will be different organs and different degrees of adverse reactions. When liver injury occurred, the effect of Chinese medicine became worse. When skin toxicity occurs, the therapeutic effect of ear acupuncture, acupuncture, and traditional Chinese medicine soaking will also be reduced, and it is difficult to achieve the ideal therapeutic effect.

In summary, immunotherapy, especially the application of immune checkpoint inhibitors, has brought hope for the treatment of triple-negative breast cancer, but it is inevitable that there will be different degrees of adverse immune reactions, which will directly or indirectly affect the effect of other immunotherapies and reduce the clinical cure rate. There are many reasons for these problems, which cannot be solved by a single method. How to recognize and deal with immune-related adverse reactions is related to the safety and sustainability of patient treatment, which needs to be taken seriously and handled with caution.

Outlook

Treatment for breast cancer has raised concerns because it is one of the most prevalent malignant tumors in women, particularly when it comes to triple-negative breast cancer. Treatment for triple-negative breast cancer is challenging due

to the lack of useful targets. Immunotherapy for triple-negative breast cancer is currently being actively used, and optimal outcomes for triple-negative breast cancer have been attained when immunotherapy is paired with chemotherapy or other treatments. The clinical cure rate has increased dramatically as a result of the widespread use of immunological checkpoint, adoptive immunotherapy, tumor vaccines, combined treatment of traditional Chinese and Western medicine, and other techniques used singly or in combination. Immunotherapy does, however, have several unresolved issues, including immunotoxicity, low immune expression, and other deficiencies. Moreover, it is challenging to help more patients with triple-negative breast cancer, so we must continue to be aware of these issues and work to find solutions.

Acknowledgments

This research was supported by the Hebei Provincial Health Commission, Key Science and Technology Research Program, (Grant no. 20220962); Hebei Provincial Administration of Traditional Chinese Medicine, 2023 Chinese Medicine Scientific Research Project, (Grant no. 2023045); Hebei Provincial Health Commission, Hebei 2024 Medical Science Research Project, (Grant no. 20240282); Hebei Provincial Administration of Traditional Chinese Medicine, 2024 Chinese Medicine Scientific Research Program, (Grant no. 2024023); National Natural Science Foundation of China, (Grant no. 81603412).

Disclosure

The authors declare that they have no conflicts of interest in this work.

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