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The immunotherapy progression of breast cancer

Yilin Yin

Mianyang Middle School, Sichuan, China

Xwch05@mtc.edu.cn

Abstract. Every year, nearly forty thousand people lose their lives to breast cancer. It has become a leading cause of death for women. Researchers have not yet identified the precise cause of cancer. In the past, breast cancer treatment was commonly performed with surgery or chemotherapy. With advances in immunotherapy and technological innovations, a variety of valuable emerging immunotherapies have emerged, including tumor vaccines, adoptive immunotherapies, there is also a class of drugs called immune checkpoint inhibitors. For example, studies have shown that autologous dc vaccines for breast cancer can improve 5-year survival. In addition, the combination of immune cells and cytokines also showed a high effect on killing tumor cells. For example, the combination of lymphokine activated killer cells (LAK) and interleukin-2 (IL-2). However, the side effects should not be ignored. This article discusses recent advances in immunotherapy for breast cancer. Symptoms, etiology, pathogenesis, and prevalence of breast cancer are described separately. It also explains the immunological mechanisms of existing immunotherapeutic modalities and considers the limitations of the current immunotherapy for breast cancer, giving a reference for future development. With the aim of informing future academic research on immunotherapy for breast cancer, the current approaches and vaccines for the treatment are examined in this paper.

Keywords: Immunotherapy, Breast Cancer, Treatment.

1. Introduction

Breast cancer is a disease in which cells in the breast grow abnormally. These cells can divide more quickly than the normal cells and continue accumulating and then there will be a lump or mass. Breast cancer can spread out of the breast if patients cannot find them on time and cause more new problems. For example, they will transfer to other organs like the bone, liver, lung, or even brain. For this reason, the breast cancer can hardly be cured completely [1]. Breast cancer is divided into a variety of subtypes based on different types of breast cells, including but not limited to ductal carcinoma in situ, breast Paget's disease, inflammatory breast cancer, hemangiosarcoma, invasive lobular carcinoma, male breast cancer, lobular carcinoma in situ, and recurrent breast cancer. These subtypes represent the diversity of breast cancer at the cellular level.

About 297,790 women will receive invasive breast cancer diagnoses in 2023. 55,720 new cases of DCIS will be identified. Nearly 43,700 people will lose their lives because of breast cancer. It has become the main reason that can cause the deaths of women. Africa and Asia will account for 63% of all deaths in 2020. Although the incidence is higher in developed regions, the number of deaths is lower than in less developed regions [2]. Women unlucky enough to contract breast cancer in low- and many

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middle-income nations have lower survival rates than women in comparable circumstances who reside in high-income regions [3].

There are many factors that can induce breast cancer, whether by themselves or by the environment, such as age, genetics, diet, alcohol, overnutrition, obesity and etc. So far, scientists have not found the exact factor that could cause breast cancer directly. A breast bulge or thickness may be one of the signs. b. A change in size, shape, or appearance. c. Dimpling or other changes to the skin over the breasts. d. A newly flipped nipple. e. Shedding, crusting, or scaling of the skin over the breast. f. The breast skin becomes sunken or reddened. The breast cancer usually starts from the proliferation of the ductal [1]. The process of proliferation usually begins with the common epithelial hyperplasia, then the nontypical proliferation, and then to intraductal carcinoma. If the tumor cells break through the basement membrane, an invasive carcinoma is formed, which is the whole process of breast cancer development.

This paper introduces the immunotherapy progression of breast cancer, compares different kinds of treatment, and focuses on the three kinds of immunotherapy strategies. Despite significant developments in endocrine therapy, HER2 therapy, and chemotherapy during the previous few decades [4]. The study reviews current approaches and vaccines for breast cancer immunotherapy to explore the recurrence and metastasis of breast cancer, it provides a reference for the study of breast cancer immunotherapy.

2. Background of existing immunotherapy strategies

The immune system and malignant cells often coexist in a dynamic equilibrium. Immunotherapy aims to improve the immune response and destroy the ability of cancer by overcoming the mechanism that tumor cells escape and inhibit from the immune response. In the early stage of the cancer, dendritic cells mature and process the antigens. Then they submit the antigens to the CD4 cells and the CD8 cells. This process can result in complete tumor rows investing [5]. Cancer immunoediting has three parts: equilibrium, and escape. During the clearance stage, the immune system detects and gets rid of tumor cells. Elimination may be complete or incomplete. If immune cells cannot kill all the tumor cells, the tumor cells may enter a dormant state. They can avoid the attack from the immune system while tumor cells evolve and accumulate drug-resistant mutations that regulate the expression of tumor antigens. As soon as they complete the above steps and evolved to suppress immunity, they will release the immunosuppressive molecules to induce immune cell depletion. Three kinds of immunotherapy include passive immunotherapy (including adoptive cell therapy), active immunotherapy (including various tumor vaccines), and nonspecific immunomodulator therapy. Active immunotherapy of tumors mainly includes tumor vaccines, which use tumor cells or tumor antigen substances to immunize the body, so that the host immune system can produce anti-tumor immune response against tumor antigen, so as to prevent tumor growth, metastasis and recurrence. Passive immunotherapy of tumors is the passive transfer of immune agents or cells with anti-tumor activity to the patient, allowing effector factors to attack tumor cells in the patient. For example, the application of various monoclonal antibodies, monoclonal antibodies can activate the complement and ADCC effect, etc., and quickly attack tumor cells in vivo. Such as the common targeting breast cancer Her-2 trastuzumab and so on. Non-specific immunomodulators, mainly various cytokines, clear tumor cells by stimulating immune cells. Common cytokines such as IL and IFN can be used to intervene in prostate cancer.

3. Tumor vaccine for breast cancer

Tumor vaccines have two functions: prevention and treatment. The former prevents the occurrence of specific tumors by inducing immune memory in healthy individuals after receiving the vaccine, while the latter controls tumors by strengthening or activating the patient's own immune system. Most of them exert therapeutic effects by activating specific CD8+T cells. The TNBC vaccines currently in the preclinical research stage mainly include cancer testicular antigen vaccines, personalized peptide vaccines (PPV), derived peptide vaccines, and run-related transcription factor 2 (RUNX2) dendritic cell (DC) vaccines [6]. In a unique clinical trial for seven patients with stage II-IV HER2-overexpressing breast cancer, after surgery and adjuvant therapy, they received autologous dc injections produced by pulses of peptides produced by HER2 intracellular domains. After a median follow-up of five years, all

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seven subjects (six of whom received HER2-specific antibodies) were healthy [4]. With the deepening of the understanding of tumor occurrence and development, more and more therapeutic vaccines will enter the pre-clinical research in the future. This is why it is important to understand the mechanism of tumorigenesis and the related treatment.

4. Adoptive immunotherapy for breast cancer

Adoptive immunotherapy aims to inject sensitized lymphocytes with specific immunity or their products (such as transfer factors and immune nucleic acids) into immunocompromised individuals (such as tumor patients) to enhance anti-tumor immunity. Common types of immune cells include cytokine-induced killer cells (CIK), lymphokine-activated killer cells (LAK), tumor-infiltrating lymphocytes (TIL), chimeric antigen receptor (CAR) T cells, cytotoxic T lymphocytes (CTL), and killer cells activated by anti-CD3 monoclonal antibodies (CD3AK).

Lymphokine activated killer cells (LAK) and interleukin-2 (IL-2) are widely used in the treatment of human cancer. Induced by high doses of IL-2 and other cytokines, they can lyse the tumor cells. However, this kind of treatment is highly toxic-Severe fluid retention was the major side effect. LAK cells have shown good efficacy mainly in the treatment of renal cell carcinoma, malignant melanoma and non-Hodgkin lymphoma, but relatively poor efficacy in the treatment of other tumor types.

Tumor-infiltrating lymphocytes (TIL) is the isolation of tumor-infiltrating lymphocytes from tumor tissue. It was cultured in vitro, waited to proliferate, and then infused and the high dose of IL-2 back into the body in order to cause significant anti-tumor ability [7]. In 2017, Lee et al. [8] found that TIL can react with autologous tumor cells and demonstrate the use of ex vivo amplified TIL as a viable option for breast cancer patients with immunotherapy.

Treatment using chimeric antigen receptor (CAR) T cells showed specificity in each patient. The CARs bind to cancer cells in response to certain antigens or proteins that are present on their surface. They are made by extracting T cells from the patient and genetically altering them in a lab. This treatment has achieved remission rates of up to 80 percent for blood cancers over the past few years. However, it has not seen the same excellent results in solid tumors and this treatment is expensive, Yescarta and Kymriah cost $475,000 (€400,000) and $373,000, respectively [9].

The vast majority of cytokine-induced killer cell (CIK) cells belong to CD3+CD56+ T cells, which have the characteristics of anti-tumor T lymphocytes and natural killer cells that are not restricted by MHC. These cells can directly destroy tumor cells. Activated CIK cells produce a lot of cytokines, which can both suppress and kill tumor cells. They have a broad tumor-killing range, rapid proliferation rates, high levels of killing activity, and little side responses. As a result, these cells are advantageous for use in cancer immunotherapy. According to Pan et al.'s research [10], CIKs are a successful treatment option for TNBC patients who have lymph node positive, high TNM staging, and subpar pathological grading.

The primary effector cells of human cellular immunity in general and one of the primary effector cells used in tumor immunotherapy are cytotoxic T lymphocytes (CTL), which is also called cytotoxic T lymphocytes. These cells specialize in secreting a variety of cytokines that are involved in immune function. They can kill specific antigens such as viruses and tumor cells, and together with natural killer cells play an important role in antiviral and anti-tumor immunity of the body. The mechanism of action of CTL mainly includes two aspects: releasing perforin/granzyme to kill target cells and mediating target cell apoptosis through FASL. Perforin, also known as pore-forming protein (PFP), is the main toxic protein for cytotoxic T cells (CTL) and NK cell killing. It plays an important regulatory role in autoimmune, antiviral, and anti-tumor immunity, and is an important immune regulatory and effector molecule. Granulase is an exogenous serine protease that is produced from cytoplasmic particles that are released by natural killer cells (NK) and cytotoxic lymphocytes (CTLs). Granulase enters cells and, under the influence of its content release, leads to cell apoptosis. FASL is a cytokine that can bind to the death receptor TNFRSF6/FAS, mediating apoptosis caused by cytotoxicity during T-cell development. After CTL cells recognize target cells, the high-level FASL expressed on the cell surface recognizes each other with FASL on the target cell surface, triggering the apoptosis program inside the target cell through FASL, causing programmed cell death of the target cell. According to Katsuta et al., despite the

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presence of tumor mutation load (TMB), high FHS (CD8A, GZMB, and CXCL10 gene expression levels) in patients with triple-negative breast cancer (TNBC) implies better long-term survival and enhanced anti-cancer immunity [10, 11].

Monoclonal antibody-activated killer cells (CD3AK) have become the most concerned tumor effector cells in tumor AIT research after LAK and TIL due to their advantages such as long survival time, low dosage of exogenous IL-2, and superior anti-tumor effects in vitro and in vivo compared to LAK cells. The precursor cells of CD3AK cells cultured in vitro are derived from mononuclear cells isolated from organs such as human umbilical cord blood, lymph nodes, peripheral blood, and spleen. Under appropriate temperature and pH conditions, they are activated by CD3McAb and combined with IL-2 to become killer cells with immune activity and cell lysis characteristics. Compared with LAK cells and TIL cells, CD3AK cells have advantages such as strong amplification ability, longer in vitro survival time, high cytotoxic activity, strong ability to secrete lymphatic factors, and they can fight tumors well in vivo or in vivo. Therefore, their clinical application has great prospects [12].

5. Immune checkpoint inhibitors for breast cancer

Immune checkpoints are a type of immunosuppressive molecule that regulate the intensity and breadth of immune responses through ligand/receptor interactions on T cells, thereby reducing damage to normal tissues. Overexpression or enhancement of immune checkpoint molecules can inhibit human immune function, because of this, the tumor cells will activate the escape system. Immune checkpoint inhibitors include cytotoxic T lymphocyte-associated protein 4 (CTLA4) and PD-1/PD-L1 inhibitors. Atezolizumab, an anti-PD-L1 antibody, is a widely studied antitumor drug. Its single use in the treatment of TNBC has good tolerance and sustained clinical efficacy. CTLA4 is a T cell transmembrane receptor that competes with CD28 homologous proteins to bind B7 molecules [13]. The CTLA4 inhibitor Ipilimumab and the PD-1 inhibitor Tremelimumab have shown some progress in treating solid tumors. Ipilimumab can promote T cell activation by binding to IgG receptors of human white blood cells, triggering antibody dependent cell-mediated cytotoxicity (ADCC) and reducing the proportion of regulatory T cells (TREGs) [14]. In the clinical trial NCT02527434 using trammelumab as the monotherapy, the ORR of 12 patients who were suffering from TNBC was 8.30%, and the MOS was 12.88 months [15].

6. Challenge and improvement

With the development of tumor molecular biology and tumor immunology, it has been possible to culture a variety of specific and non-specific anti-tumor effector cells in vitro, especially the successful cultivation of tumor-specific CTLs, which enables the combination of tumor-specific immunotherapy. However, the efficacy of immunotherapy is affected by a variety of factors, such as cellular senescence, defective effector cells, excessive tumor load, and therapeutic injury. These issues need to be addressed in future studies. Understanding the mechanism of tumor immune escape, cellular immunotherapy plays a crucial part in tumor treatment when combined with conventional therapy and gene therapy. Immunotherapies, such as immune checkpoint blockade, CART cell therapy, and cancer vaccines, have currently shown some promise, but they are not without drawbacks, including high cost, poor immune response rates, significant individual variability, a lack of potent anti-tumor effects, and adverse effects. Nanomedicines have the potential to significantly increase the number of patients for whom immunotherapy is effective by regulating anti-tumor immune responses and changing the tumor microenvironment. Nanomedicines can target the peripheral immune system, inhibit immunogenic cell death in tumor cells, and lessen harmful immune-related consequences. Clinical treatments combining nanomedicines with immunotherapy began more than 20 years ago, in which the combination of autoprotein-bound paclitaxel and atelizumab for TNBC has gained approval from the FDA [16].

7. Conclusion

Breast cancer is the biggest cause among women worldwide after lung cancer. Until now, scientists have not found a clear cause of cancer. Tumor vaccines that eradicate tumor cells are an attractive option, and

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while progress has been made in current studies, none of the vaccines have shown significant benefits. The limited anti-tumor activity and complex preparation process of LAK and TIL have limited their clinical application. At present, anti-TNBC research about CAR-T cells is mostly in the preclinical research stage. CIK cell immunotherapy and CD3AK immunotherapy may be valuable options to treat breast cancer. However, there are plenty of issues that deserve to be considered. The lack of sustained anti-tumor immunity stimulated by vaccines, the slow onset of immunotherapy, the long duration of the treatment process, as well as the side effects of the treatment process, and the high price of the treatment need to be progressively addressed. In the future, humanity can anticipate faster research and clinical advancement as immunotherapies become more advanced. These developments will lessen patient suffering, lower healthcare expenses, and enhance therapy. Breast cancer immunotherapy will help more individuals as standard medicines and more and more treatments that combine immunotherapy with them become available.

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