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Immune Checkpoint Inhibitors in Breast Cancer

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Abstract. The incidence of breast cancer has risen dramatically over the past few decades and has become the most common malignancy in women. By 2040, it is expected that there will be more than 3 million new cases of breast cancer and more than 1 million deaths per year. The incidence of breast cancer has risen dramatically over the past few decades and has become the most common malignancy in women. By 2040, it is expected that there will be more than 3 million new cases of breast cancer and more than 1 million deaths per year. Immune checkpoint therapeutics was significant technological breakthrough on cancer treatment programs. It uses the body's immune system targets and eliminates cancer cells. This therapy maintains self-tolerance and modulates the immune response to minimize tissue damage during infection. This therapy inhibits immune checkpoints such as PD-1, PD-L1, and CTLA-4, which tumors exploit to evade immune detection. By blocking these pathways, immune checkpoint inhibitors can reactivate T cells, enabling them to recognize and attack breast cancer cells. This essay will explain how does checking for inhibitors help T cells recognize the breast tumor cells, and some drugs specialize in PD-1 and CTLA-4.

Keywords: Breast cancer; immune checkpoint inhibitor; PD-1; PD-L1; CTLA-4.

1. Introduction

Breast cancer, a 2nd most common cancer worldwide, its 1st cancer in women. It is a type of cancer that occurs almost exclusively in women, but men can also get breast cancer. Incidence of breast cancer among women is high, in 2022 alone, there was more than 2,296,840 cases of breast cancer worldwide. In United States the likelihood of acquiring breast cancer at some point in her life is around 13% which means a one in eight risk of developing breast cancer. But what is surprise, the mortality of breast cancer is only 2.5% which means most of the patient can survive pass 5 years after they get breast cancer [1]. With development of immune check point inhibitors in pass few years, it highlights the potential of immunotherapy and become more and more important, and it has lot of strengths compared with radiotherapy which may lead to durable responses in some patients, even after the treatment is stopped. This is unlike traditional chemotherapy, where benefits typically end once treatment ceases. This differs from standard chemotherapy, in which advantages often terminate after treatment is discontinued. Also, side effects are usually less frequent than with conventional chemotherapy, and most of the side effects can be control by the doctors (Fig.1) [2].

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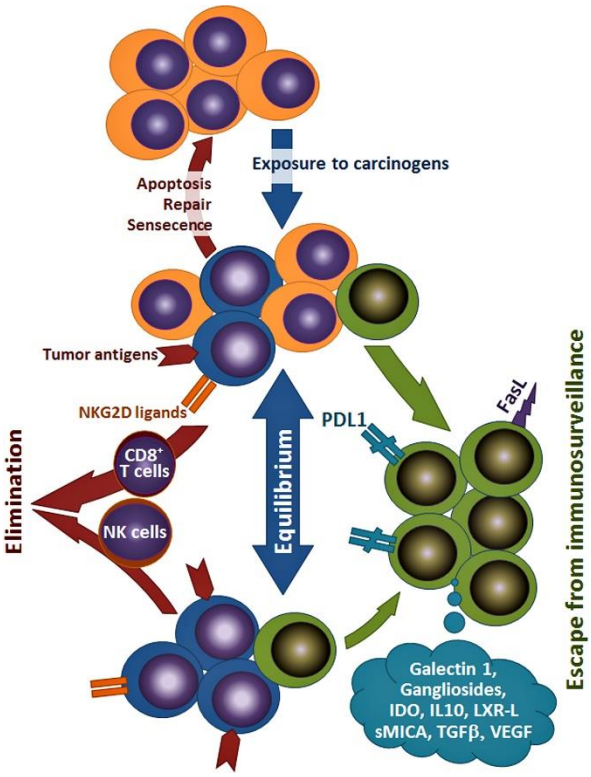

Figure 1. Schematic of immunoediting of cancer [2].

2. Role of immune system in breast cancer

Immune system plays important role in the immunotherapy, in early stage when a tumor is present or damaged than the danger signals in the tumor microenvironment activate the innate immune system like damage-associated molecular patterns DAMPs and pathogen-associated molecular patterns PAMPs. Those molecules triggers activation of the immune system, and at this point acute inflammation is rapidly initiated. Acute inflammation will attracting immune cells including neutrophils, macrophages, and natural killer (NK) cells to the tumor site. When the immune cells reach to the tumor place, they will release cytokines and chemokines that directly attack and kill tumor cells. Also, activated macrophages can induce tumor cell death by secreting tumor necrosis factor (TNF-α) and other cytokines and NK cells can lyse and kill tumor cells by identifying aberrant surface marks on them [3]. After tumor cell death, the antigens released retaken by dendritic cells, and the signals in the acute inflammatory milieu such as pro-inflammatory cytokines (IL-1, TNF-α, IL-6), chemokines, DAMPs (HMGB1). They can contribute to the maturation of DCs. Mature DCs then migrate to lymph nodes to show tumor antigens to T cells. After DCs show tumor antigens to T cells in lymph nodes, which it will activate tumor-specific T cells. These T cells include CD8 cytotoxic T cells are activated to enter the tumor site and recognize and kill residual tumor cells [2]. If acute inflammation does not completely clear the tumor, then the inflammation may persist and fail to enter the repair and regression phase and turn in to the chronic inflammation. In chronic inflammation will be dominate by the monocytes, macrophages, lymphocytes (especially T and B cells) and fibroblasts, but macrophages have negative effect in chronic inflammation, because it will continue to secrete pro-inflammatory factors, also may cause tissue damage and fibrosis. In the chronic inflammation those pro-inflammatory cytokines persistent expression just like TNF- α, IL-6, IL-1 β and anti-inflammatory mechanisms like IL-10, TGF- β failing make inflammatory response continues to be active and cannot be effectively terminated. This signaling imbalance exacerbates tissue damage. In the tumor microenvironment, chronic inflammation by secreting pro-growth factors and matrix remodeling enzymes, what is lucky most of the breast cancer was benign tumors which mean the breast tumor cells will not easily dispersal to other organization [4]. In the context of chronic inflammation, persistent immune cell infiltration and secretion of inflammatory factors lead to

repeated tissue damage and repair, ultimately leading to fibrosis and the fibrosis will really hurt body. And the tumor microenvironment may be altered to create an immunosuppressive state. For example, an increase in regulatory T cells and myeloid-derived suppressor cells inhibits the activity of anti-tumor T cells, thus helping the breast tumor to evade immune surveillance. The consequences of chronic inflammation were heavy, first in chronic inflammatory environments, inflammatory mediators and cytokines promote the shaping of the tumor microenvironment which mean there will induction of neovascularization which make breast tumor cell survival and proliferation and the chronic inflammatory will also causes DNA damage and gene mutations.

3. Recent clinical advances in breast cancer

What is exciting is recent clinical advances in breast cancer treatment has the significant progress, particularly with the development of immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways. This new progress opening new avenues of treatment for breast cancer patients, especially in cases where chemotherapy treatment is not effective [5]. These therapies have already shown the promising results in malignant breast cancers, such as triple-negative breast cancer (TNBC), this cancer is characterized by the absent of estrogen receptors, progesterone receptors, and small amounts of HER2 protein, so many of traditional therapy doesn't woke well. But immune checkpoint inhibitors offer a new therapeutic option. Focus on CTLA-4 check point, there are two main medicines which are Tremelimumab and Ipilimumab. Firstly, Tremelimumab is a fully human monoclonal antibody targeting CTLA-4, even this kind of drug has been studied primarily in melanoma, research has expanded to breast cancer, particularly in combination with other therapies. The mechanism of Tremelimumab is to blocks CTLA-4, preventing it from interacting with ligands CD80 and CD86 on antigen-presenting cells [6]. This blockade enhances T-cell activation and proliferation and to make the checkpoint proteins on T cells inactive. Another CTLA-4 inhibitor, ibritumomab, is approved for the treatment of melanoma but is also being studied for the treatment of breast cancer, like Tremelimumab, ibritumomab blocks CTLA-4 to boosting the immune system's ability to attack cancer cells. Ipilimumab shows promise when used in combination with other immunotherapies such like nivolumab. The rationale for combining ibritumomab with other checkpoint inhibitors is that their mechanisms of action are complementary: CTLA-4 blockade enhances T-cell initiation, while PD-1 inhibition releases the "brakes" on T-cells in the tumor microenvironment, making the immune response more effective [7]. Next, PD-1 cheek point have three main type of drugs Avelumab, Atezolizumab and Pembrolizumab. First, Avelumab is a fully human monoclonal antibody directed against PD-L1, it was initially approved for the treatment of metastatic Merkel cell carcinoma and later for the treatment of uroepithelial carcinoma. At breast cancer (especially TNBC), avelumab has shown potential, especially when combined with chemotherapy [8]. Chemotherapy can increase PD-L1 expression in tumor cells, making them more susceptible to PD-L1 blockade by avelumab. Clinical trials of avelumab have focused on combining it with chemotherapeutic agents such as paclitaxel, and the study aims to determine whether adding avelumab to standard chemotherapy improves outcomes for patients with advanced or metastatic breast cancer. Early results are really well, with some trials showing an increase in progression-free survival for patients receiving the combination therapy [9]. Another PD-L1 inhibitor, atilizumab, is the first checkpoint inhibitor approved for the treatment of breast cancer. The drug is approved in combination with albumin-bound paclitaxel for the treatment of patients with PD-L1-positive metastatic TNBC. The approval was based on the IMpassion130 trial, it showed that the combination of atilizumab with albumin-bound paclitaxel also significantly improved progression-free survival in patients whose tumors expressed PD-L1, compared to chemotherapy alone. what is the atelizumab works is suppressing PD-L1 on tumor cells and tumor-infiltrating immune cells, preventing it from attaching to PD-1 on T cells and this blockage allows the T cells to remain active and continue to attack the tumor cells [10]. And the last one this Pembrolizumab. Pembrolizumab is also a PD-1 inhibitor but has been approved for the treatment of several cancer types, including TNBC. In Breast Cancer, Pembrolizumab Approved in combination with chemotherapy for patients with locally recurrent, unresectable and TNBC. In addition to its use in metastatic disease, pembrolizumab has

shown efficacy as a neoadjuvant therapy. At the KEYNOTE-522 trial evaluated the effectiveness of pembrolizumab in combination with chemotherapy as neoadjuvant therapy for early stage TNBC and the results showed a significant increase in the rate of complete pathological remission, which shown no residual invasive cancer in the breast or lymph nodes at the time of surgery [11].

4. Conclusion

The introduction of immune checkpoint inhibitors has revolutionized the treatment of breast cancer, particularly TNBC, a subtype that has historically had poor outcomes and limited treatment options. These therapies have prolonged patient survival and provide new hope for patients for whom conventional therapies have not worked. Something is interesting is that not all patients respond to checkpoint inhibitors, and the reasons for this discrepancy are not fully understood. Further studies will also focus on expanding the use of immune checkpoint inhibitors to other breast cancer subtypes beyond TNBC. HER2-positive and hormone receptor-positive breast cancers respond poorly to immunotherapy, but ongoing studies are evaluating whether combining checkpoint inhibitors with HER2-targeted therapies or endocrine therapies improves prognosis in these patients.

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