Combination Strategies for PD-1-Based Immunotherapy in Breast Cancer

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Abstract. Immunotherapy for breast cancer has shown some advantages in clinical practice. The PD-1/PD-L1 immune checkpoint shows a notably high incidence of positive expression in triple-negative breast cancer cases. Interestingly, this expression doesn't seem to align with the clinical attributes of the disease. The presence of tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) in the disease's environment can be a major breaker, even if PD-1/PD-L1 inhibitors have shown promising outcomes in the fight against breast cancer. It's like trying to win a game of chess with just one pawn when the rest of your opponent's army is intact. Simply relying on a single inhibitor to do the heavy lifting just doesn't cut it in this fight. Recent research on PD-1/PD-L1 expression and its connection to the development of breast cancer is combined in this paper. With an emphasis on developments in integrating immunotherapy approaches, it evaluates various PD-1/PD-L1 immunotherapy blends in conjunction with other breast cancer treatments. The piece delves into the intricacies of various integrated treatment modalities and their advancements in clinical trials, seeking to establish a solid theoretical foundation and practical insights for the impending era of combined immunotherapy in breast cancer treatment.

Keywords: PD-1/PD-L1, Tumor microenvironment, Breast cancer, Immune checkpoint blockade, Combined treatment.

1. Introduction

Breast cancer, particularly triple-negative and metastatic forms, ranks among the most common malignant tumors affecting women. However, there are still some problems with the traditional treatment. The characteristics of triple-negative breast cancer (TNBC), such as high heterogeneity, treatment of drug resistance, severe toxicities, and adverse reactions from chemotherapy, make TNBC the most challenging kind to control currently. Immunotherapy has shown a lot of promise as immunology has advanced. The PD-1/PD-L1 pathway notably influences cancer immune escape regulation. PD-1 is mainly located on activated T cell surfaces, while PD-L1 exists on tumor cells. When combined, they prevent T cells from doing their job and let tumor cells get past the body's defenses. T cells can recover their anti-tumor function by using PD-1/PD-L1 inhibitors, which stop PD-1 and PD-L1 from cooperating. Ongoing clinical research validates the substantial extension of breast cancer patients' survival through PD-1/PD-L1 immunotherapy. However, due to the tumor microenvironment (TME) of breast cancer being highly heterogeneous, TAMs and Tregs significantly suppress immune responses, leading to poor efficacy of PD-1/PD-L1 inhibitors. Currently, researchers are actively exploring the combination of PD-1/PD-L1 inhibitors with other treatments to enhance efficacy. This article reviews the recent studies on the expression and clinical significance of PD-1/PD-L1 in breast cancer, based on the current immunotherapy combination strategies, and summarizes a series of immunotherapy regimens for breast cancer. The piece at hand delves into the integration of this inhibitor with chemotherapy, targeted therapies, and anti-angiogenic agents in the fight against breast cancer. Its primary aim is to offer a comprehensive reference for future research and clinical applications.

2. The mechanism and inhibitors progress of PD-1/PD-L1

2.1. PD-1/PD-L1 in breast cancer microenvironment

Activated T and B cells are the main source of PD-1, whereas tumor cells express the PD-L1 ligand. By interacting with PD-L1, PD-1 effectively inhibits T cell function, enabling the tumor to evade the immune system's grasp. Therefore, by interfering with the PD-1/PD-L1 axis, we can stimulate the T cells and generate a more robust immune response.

In peripheral malignancies, PD-1 interacts with PD-L1 to inhibit T cell activation and proliferation by inhibiting the PI3K-AKT-mTOR and Ras-MEK-ERK signal transduction pathways. Consequently, T cells succumb to apoptosis, diminishing their efficacy in eliminating cancer cells (Figure 1) [1].

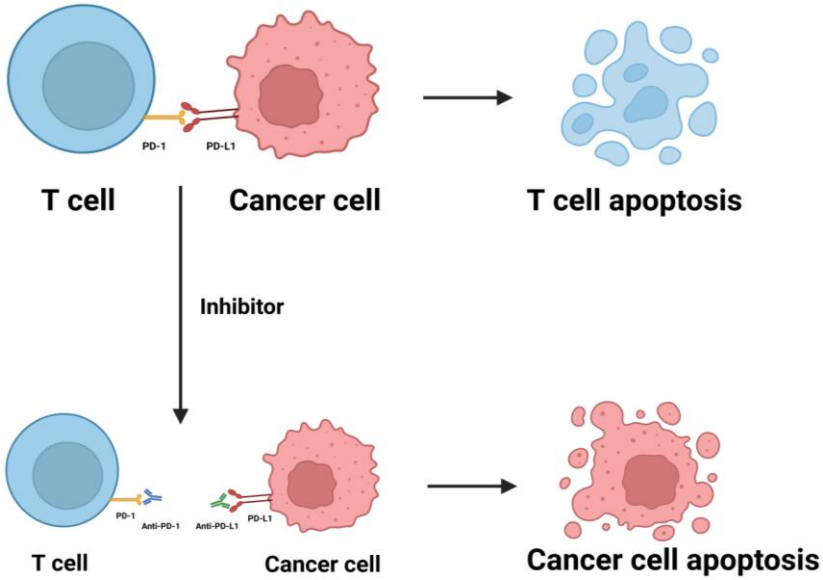

Figure 1. The effect of PD-1/PD-L1 inhibitor

2.2. PD-1/PD-L1 in triple-negative breast cancer

In the pathological examination of TNBC, human epidermal growth factor-2 (HER-2), progesterone receptor (PR), and estrogen receptor (ER) are all negative for malignancy. The prognosis for the existing therapeutic approaches is poor, and it is simple for TNBC to spread. TNBC is the most difficult kind of breast cancer because there are not any treatment targets for it. 20% PD-L1 expresses of TNBC patients [2]. The PD-1/PD-L1 inhibitory pathway lets PD-L1 expression positive on the tumor surface to enable tumor cells to complete immune escape. Zhou's study pointed out that TNBC patients using PD-1/PD-L1 inhibitors provided significantly better treatment results in the adjuvant treatment of non-metastatic TNBC patients [3].

2.3. Progress of PD-1/PD-L1 inhibitors in clinical immunotherapy of breast cancer

These inhibitors effectively inhibit the engagement of PD-1, PD-L1, and PD-L2 on cancer cells, facilitating T cell detection of tumor immune evasion and triggering anti-tumor reactions. Inhibitors prevent tumor cell immunological evasion and rejuvenate T cell anti-tumor response by obstructing the PD-1/PD-L1 axis. Therefore, it enhances the immune system's capacity to eliminate cancerous cells [4]. Based on Qi's study data, for the single PD-1/PD-L1 inhibitor employed in treating breast cancer, the full response rate stood at 1.26%, the partial response rate was 7.65%, the objective response rate (ORR) was 9.85%, and the disease control rate (DCR) was 18.33%. The overall survival rate at one year was 43.34%, while the progression-free survival rate at six months was 17.24%. The occurrence of immune-related adverse effects, or irAEs, hovered around a rate of 14.75%, whereas the overall rate of adverse effects, AEs, reached 64.18%. Issues like anemia, autoimmune hepatitis, and hypothyroidism topped the list as the most common setbacks [5].

Tumor microenvironment may affect PD-1/PD-L1 inhibitor effectiveness. Tregs and myeloid-derived suppressor cells (MDSCs) are two examples of immunosuppressive cells. These cells exhibit immunological checkpoint molecules like PD-1 and CTLA-4 and release inhibitory cytokines including TGF-β and IL-10. T cell inhibition lessens the therapeutic effect of these medications. Moreover, suppression of anticancer immune responses by Tregs can lead to immune evasion, tumor proliferation, and the spread of cancer cells [6].

3. PD-1/PD-L1 immunotherapy combined with other strategies

3.1. PD-1/PD-L1 inhibitor combined with chemotherapy strategy

A randomized phase III clinical trial for non-metastatic TNBC is called KEYNOTE-552. The pathological complete response (pCR) rate in this trial increased from 30% to 50% with chemotherapy alone to 65% when pembrolizumab was added to chemotherapy as a neoadjuvant treatment [7]. The overall survival rate after 5 years of combined strategy (KEYNOTE-552) reached 86.6%, compared to 81.7% of the patients receiving chemotherapy alone [8]. The modified KEYNOTE-552 uses doxorubicin plus cyclophosphamide (AC) administered once every 3 weeks. The dose-dense AC (ddAC) showed a higher overall survival (OS). The study shows that in this modified strategy, ddAC is safe and reliable. The efficacy has been improved [9].

In the ground-breaking KEYNOTE-355 study, scientists investigated the effectiveness of treating metastatic triple-negative breast cancer by combining the PD-1 blocker pembrolizumab with a powerful combination of chemotherapy medications, carboplatin, gemcitabine, and paclitaxel. The results were nothing short of impressive, as it more than doubled the disease-free survival time, from 5.6 to 9.7 months. This was especially true for those patients whose tumors were positively expressing PD-L1 with a CPS score of 10 or better [10].

The combination of atezolizumab and albumin-bound paclitaxel significantly increased the median progression-free survival rate for TNBC patients receiving treatment, rising to 7.2 months from the usual 5.5 months, as demonstrated in Schmid's study. The method greatly increased the amount of time TNBC patients may enjoy without their cancer progressing [11].

3.2. PD-1/PD-L1 inhibitor combined with radiotherapy strategy

The PD-1/PD-L1 inhibitor, in synergy with radiation, activates immunogenic cell death, enhancing the cytotoxic T cells' immunological reaction. Radiotherapy can also cause abscopal effect (AE), activating the systemic anti-tumor immune response. This leads to an increase in immune activity in other regions and inhibition of the growth of metastasis in other regions [12]. The anti-tumor action of radiation therapy can increase the effectiveness of PD-1/PD-L1 inhibitors. The study by Voorwerk demonstrated that the treatment of TNBC with PD-L1 inhibitor combined with radiotherapy reveals that in a certain proportion of patients, the treatment of combining inhibitors with radiotherapy can increase the response rate and survival rate [13].

3.3. PD-1/PD-L1 inhibitor combined with targeted drug strategy

The tumor microenvironment's TAMs and Tregs in breast cancer affect inhibitor effectiveness. They may diminish the efficiency of these inhibitors. TAMs typically present M2 characteristics. TAMs secrete cytokines within the breast cancer milieu, thereby dampening immune signaling and fostering the development of new blood vessels. Currently, inhibiting the CCL2-CCR2 or CCR5-CCL-5 pathways can prevent TAM recruitment to tumors. TAMs also can be depleted by blocking CSF-1 or CSF-1R. Transforming tumor-promoting TAMs into anti-tumor agents is an additional method. It has been demonstrated that HDAC inhibitors, CD40 agonists, PI3Kγ inhibitors, and CD47 inhibitors decrease primary and metastatic breast cancer in mice and change TAMs into anti-tumor agents [14].

By encouraging the growth of Tregs in the tumor microenvironment, GARP and TGF-β overexpression in breast cancer accelerates tumor progression. Tregs can prevent naive T cells from

proliferating and differentiating, as well as prevent a range of immune cells from performing their effector tasks [15].

Tregs exhibit elevated CTLA-4 expression. Combining anti-PD-1 and anti-CTLA-4 inhibitors has been shown to increase tumor immunity. In comparison to the single therapy of α-PD-1 (RR 1.31, 95% CI 1.16-1.48) or α-CTLA-4 (RR 2.11, 95% CI 1.84-2.43), the patients undergoing the combination therapy of α-PD-1 + α-CTLA4 demonstrated a notably higher objective response rate (ORR) (RR 1.41, 95% CI 1.26-1.58) [16].

3.4. PD-1/PD-L1 inhibitor combined with anti-angiogenic drug strategy

Tumor-targeted T lymphocytes migrate from secondary lymphoid organs and penetrate tumor tissues through blood vessels according to immune checkpoint inhibitors, also known as ICIs (Immune Checkpoint Inhibitors). The increased expression of adhesion molecules and chemokines in the tumor vasculature is a sign of endothelial activation, which is necessary for leukocyte infiltration into tumor tissue. Due to angiogenesis in the tumor microenvironment, tumor blood vessels are often activated insufficiently, thus serving as a barrier to effective leukocyte recruitment [17]. By disrupting blood vessel growth, anti-angiogenesis deprives tumors of essential oxygen and nutrition. Unlocking this success hinges on suppressing the unruly angiogenesis within the tumor, enriching the tumor's surroundings with oxygen, enhancing the immune system's soldiers and their might, and stifling the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis that flourishes in the tumor's niche [18].

Incorporating this inhibitor with anti-angiogenic agents yields two primary anti-cancer benefits. For starters, these inhibitors shut down the pathway, thereby prompting T cells to attack the tumor cells. Anti-angiogenic medications diminish immunosuppressive cells and factors, increasing immune cells' anti-tumor activity. Anti-angiogenic medications, on the other hand, can alter the blood flow and blood supply to cancer areas, allowing immune cells to penetrate more deeply. Also, drugs can affect the distribution in tumor tissues, so that PD-1/PD-L1 inhibitors can better enter tumor tissues. The clinical data by Wang used the anti-PD-L1 inhibitor TQB2450 in combination with multikinase inhibitor anlotinib. The clinical efficacy showed that 3 patients (8.8%) achieved complete response (CR), 6 patients (17.6%) achieved partial response (PR), and ORR was 26.5% (95% CI, 12.9-44.4). The disease control rate (DCR) was 73.5% (95% CI, 55.6-87.1) (Figure 2) [19].

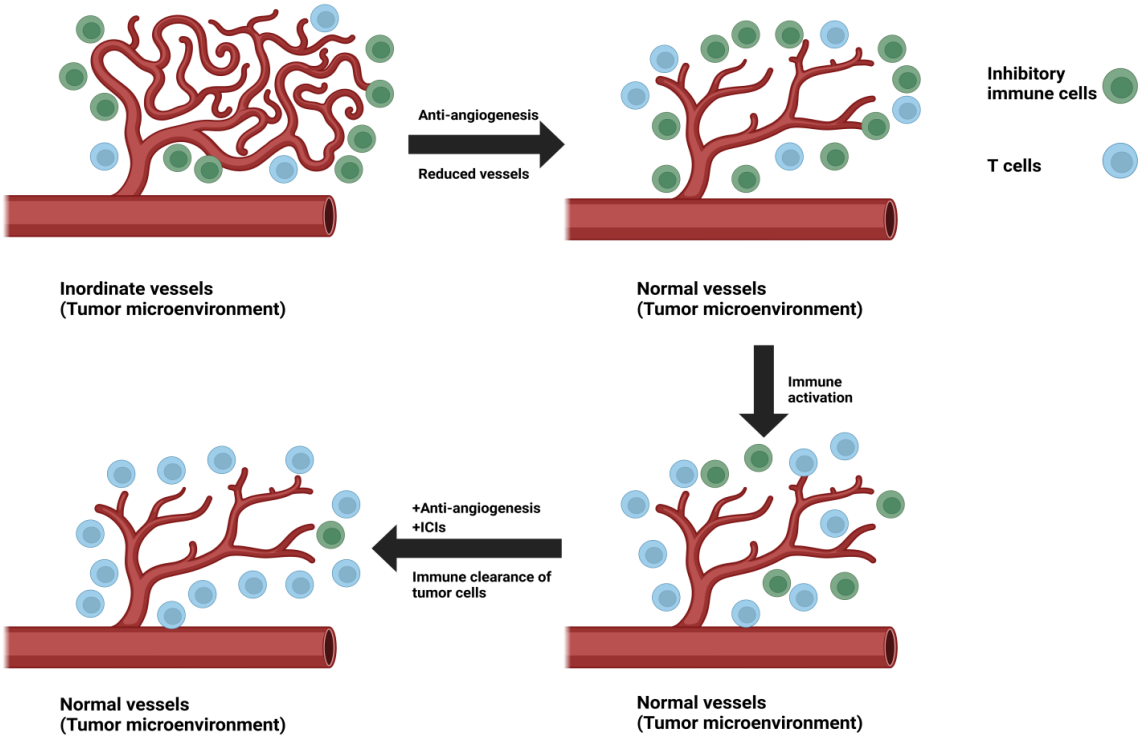

Figure 2. Mechanism of the drug combination of Anti-angiogenic and ICIs

4. Discussion

Therapeutic approaches for breast cancer have progressed from single-agent PD-1/PD-L1 inhibitors to complex combination therapies. Recent research in immunotherapy reveals the combined efficacy of radiation and checkpoint blockade therapy. Research indicates that localized radiation can elevate the abscopal effect (AE) in PD-L1-positive TNBC by as much as 28% through enhanced release of tumor-specific antigens. In the chemotherapy combination strategy, paclitaxel, toripalimab, and carboplatin (NMPA, 2024) had been approved. PD-L1 positive (CPS≥1) TNBC is now treated with immunotherapy and chemotherapy as the primary treatment option. According to clinical data, this regimen had a median progression-free survival of 7.2 months, which is 42% longer than chemotherapy alone. In targeted drug combinations, the synthetic lethal effect of PARP inhibitor and PD-1 inhibitor has attracted attention. The objective response rate (ORR) of the olaparib combination in BRCA mutated patients is about 34%, and its mechanism is related to the increase of tumor neoantigens caused by DNA damage repair.

However, combined strategies still faced challenges. First, heterogeneity in biomarker screening, with differences in PD-L1 testing criteria leading to cancer misclassification in 25% of patients. Second, the resistance mechanisms of this inhibitor are complex. The incidence of AE related to immune inhibitors increased in combination therapy, and the incidence of grade 3 or above pneumonia reached 12%. This data was significantly higher than that of single inhibitors. In the future, pay more attention to research strategies of precise treatment of types combined with other treatments to improve the accuracy and therapeutic effect of breast cancer immunotherapy.

5. Conclusion

This article introduces a novel combined therapeutic approach for clinical breast cancer centered on PD-1 immune modulation, especially triple-negative breast cancer that is resistant.

TNBC frequently shows elevated PD-1/PD-L1 expression, a finding that supports the rationale for PD-1 modulation. Limited efficacy arises from the tumor microenvironment's influence on the single PD-1/PD-L1 inhibitor's therapeutic response in breast The specifics of how combining chemotherapy boosts the impact of the inhibitor treatments are still not entirely understood. However, by integrating chemo, targeted therapies, anti-angiogenesis medications, and other methods, the treatment regimen is fine-tuned to yield improved outcomes, indeed for those suffering from triple-negative breast cancer.

There are still some limitations and deficiencies in research in this field. The immune microenvironment of breast cancer types is different. So, different combination treatment strategies should be considered. The mechanism by which the chemotherapy combination strategy increases the effectiveness of PD-1/PD-L1 inhibitor therapy is still questionable. Subsequent studies need to delve into various cocktail treatment approaches while tackling the issue of resistance and side effects associated with PD-1/PD-L1 blockers, ultimately offering more effective immunotherapy options for breast cancer sufferers.

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