The Utilisation of Immune Checkpoint Inhibitors in Triple-Negative Breast Cancer

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Abstract: For several years, surgical intervention and chemotherapy have been employed to address triple-negative breast cancer (TNBC), a heterogeneous subtype of invasive breast carcinoma. In recent years, FDA has sanctioned CTLA-4 monoclonal antibodies (mAbs) such as ipilimumab, along with PD-1/PD-L1 mAbs like pembrolizumab and atezolizumab, for the therapeutic management of multiple solid tumours, prompted by research on immune checkpoints including CTLA-4 and PD-1/PD-L1. The combination of PD-1/PD-L1 inhibitors with chemotherapy has demonstrated efficacy in the treatment of both early-stage and metastatic TNBC when immune checkpoint inhibitors (ICIs) are employed. This article compiles the mechanisms of PD-1/PD-L1 and CTLA-4 as ICIs, along with their research on monotherapy in TNBC. It also discussed how combination therapies, which include CTLA-4 and PD-1/PD-L1 inhibitors, as well as chemotherapy and immunomodulatory drugs (ICIs) can be utilised to treat TNBC. A summary of the negative outcomes of immunotherapy was also provided.

1 INTRODUCTION

Triple-negative breast cancer (TNBC), a heterogeneous subtype of invasive breast cancer (BC), does not express the progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), or oestrogen receptor (ER). About 15–25% of all cases of BC are caused by it (Michaels et al. 2024). Younger women and women of African or Hispanic heritage are more likely to have TNBC. Additionally, patients with germline *BRCA1* mutations are more susceptible to developing TNBC (Derakhshan & Reis-Filho 2022). TNBC has the greatest incidences of relapse and fatality among breast cancer subtypes and is difficult to treat because of its high intrusiveness and tendency for both regional and distant metastases (Liu et al. 2023, Leon-Ferre & Goetz 2023). Since metastatic TNBC (mTNBC) lacks specific targets, treatment options are limited, and surgery and cytotoxic chemotherapy remain the mainstays of therapy (Zhu et al. 2021). While these therapies offer some management of TNBC, their long-term effectiveness is frequently inadequate, particularly for mTNBC. This correlates with a bleak prognosis, yielding a median overall survival (OS) of around 12-18 months. (Cao et al. 2021). The use of PARP inhibitors, together with traditional protein tyrosine kinase or phosphoinositide 3-kinase inhibitors, does not significantly enhance OS (Bai et al. 2021). Thus, it is essential to investigate more potent TNBC treatment approaches.

With the advancement of immune therapy in the past few decades, immune-checkpoint inhibitors (ICIs) have shown impressive effectiveness in the curative use of several solid tumours that exhibit resistance to therapy, including gastric cancer, renal cancer, and hepatocellular carcinoma (Poniewierska-Baran et al. 2024, Lavacchi et al. 2020, Akbulut et al. 2024). ICIs function by targeting and blocking immune checkpoints, such as CTLA-4 and PD-1, from binding to their ligands on antigen-presenting cells (APCs) or tumor cells. This enhances T-cell activity, enabling them to more effectively identify and attack tumor cells (Iranzo et al. 2022). Most ICIs are monoclonal antibodies (mAbs), with the most extensively studied being the CTLA-4 antibody ipilimumab and the PD-1/PD-L1 antibodies, such as pembrolizumab (Kwapisz 2021). TNBC has a comparatively larger tumor mutational burden and more lymphocyte infiltration than other BC subgroups. This suggests that TNBC has an

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immunological microenvironment and neoantigens that provide favorable conditions for the application of ICIs in its treatment (Liu et al. 2023). Research has found that PD-L1 is overexpressed on the surface of TNBC cells, making PD-1/PD-L1 a primary target for ICI development in TNBC (Li et al. 2021). In the clinical management of TNBC, there has been enhancement made with both monotherapy and combination treatments including anti-PD-1/PD-L1 drugs. For instance, the Food and Drug Administration (FDA) authorized pembrolizumab plus nab-paclitaxel as the primary therapy for mTNBC after the KEYNOTE-355 trial proved successful. The FDA granted permission to the combination of pembrolizumab and chemotherapy for early-stage triple-negative breast cancer based on the findings of the KEYNOTE-522 study (Jin et al. 2024). Furthermore, clinical studies have assessed the anti-PD-1 medication pembrolizumab and the FDA-approved anti-PD-L1 medication atezolizumab, both in conjunction with chemotherapy (Heeke & Tan 2021). Moreover, monotherapy has demonstrated durable effects in advanced mTNBC (Won & Spruck 2020). Although ICIs have shown promise in treating TNBC, further improvements are needed in terms of prognosis and side effects. The use of ICIs in the management of TNBC was compiled in this overview, with an emphasis on PD-1/PD-L1 blockers. It discussed therapeutic strategies involving both ICI monotherapy and combination therapy, as well as the associated toxicities of ICIs.

2 IMMUNE-CHECKPOINT INHIBITORS IN TRIPLE-NEGATIVE BREAST CANCER

With the advancement of immunotherapy, ICIs have been widely employed in cancer treatment. T cell activation is negatively regulated by immunological checkpoints, which are molecules found in the immune system. They function as the immune system's 'brakes', which are crucial for preserving self-tolerance and avoiding tissue damage (Li et al. 2021). Malignant cells in cancer use immunological checkpoints to avoid immune monitoring, which helps them avoid detection and spread (Sutanto et al. 2024). To put it simply, ICIs work by inhibiting these checkpoints, which reactivate T cells so they can identify and combat cancer cells (Sutanto et al. 2024). The two most investigated targets for ICIs in TNBC at the moment are PD-1/PD-L1 and CTLA-4, with PD-1/PD-L1 inhibitors receiving more attention. CD152, another name for CTLA-4, is a transmembrane protein. Costimulatory receptors known as CTLA-4 and CD28 are present on the outermost membrane of T cells, providing activating and inhibiting secondary signals, respectively. Both receptors attach to the APC surface's B7-1/2 (CD80/86). T cells get activated when CD28 interacts with B7; however, T cells that are activated additionally produce CTLA-4, which possesses a higher attraction for B7 than CD28. Consequently, CTLA-4 often inhibits T cell activation by transmitting a suppressive signal to T cells prior to CD28-mediated activation. (Hossen et al. 2023). CTLA-4 inhibitors prevent CTLA-4 from attaching to B7, hence promoting CD28's attachment to B7 and facilitating T cell activation. Conversely, CTLA-4 inhibitors may impede the internalisation of B7 ligands by APCs, hence augmenting B7 expression and improving the binding attraction of CD28 to B7 (Wen et al. 2024). In clinical therapy, CTLA-4 inhibitors like ipilimumab are frequently employed to manage malignant melanoma. However, there are currently no FDA-approved CTLA-4 inhibitors for TNBC.

PD-1 is a type I transmembrane protein that is widely expressed on the surface of activated T cells, B cells, monocytes, and dendritic cells (Li et al. 2021). The ligands for PD-1 are PD-L1 and PD-L2, with PD-L1 being upregulated in various solid tumors. This upregulation suggests a close relationship between PD-L1 and tumor immune evasion (Li et al. 2021, Zhang et al. 2023). Tyrosine residues on PD-1 undergo phosphorylation upon binding to PD-L1 on antigen surfaces, transmitting a co-inhibitory signal. This pathway aids cancer cells in evading immune system identification by inhibiting the activation and functionality of cells such as CD8+ T lymphocytes and natural killer (NK) cells (Zhang et al. 2023). By obstructing this interaction, antagonists of PD-1/PD-L1 prevent detrimental signals from being sent and allow T cells to perform their standard anti-tumor immunological roles (Sharma et al. 2023). At now, PD-1/PD-L1 inhibiting agents, including pembrolizumab, are widely used as primary agents in the immunotherapy of breast cancer (Zhang et al. 2023). PD-1/PD-L1 has emerged as a significant target for TNBC immunotherapies due to the fact that TNBC cells express PD-1 and PD-L1 at high levels. Monotherapy and combination treatments utilising PD-1/PD-L1 inhibitors have shown

significant progress in the medical management of TNBC. Atezolizumab was authorized by the FDA in 2019 to treat PD-L1-positive, locally progressed TNBC or mTNBC that is incurable. The FDA then authorized pembrolizumab and chemotherapy in 2020 to treat individuals with PD-L1 expression positive (CPS≥10) who had locally recurrent, unresectable, or mTNBC (Li et al. 2022). Blockers of PD-1/PD-L1 and CTLA-4 both obstruct signals that diminish T cell activation. PD-1/PD-L1 inhibitors reinstate the toxicity of CD8+ T cells, while CTLA-4 inhibitors primarily influence the clonal proliferation and migration of CD4+ T cells (Zhang et al. 2023). Currently, among immunotherapeutic agents targeting TNBC, ICIs have emerged as the most effective treatment options (Wen et al. 2024). Their development holds promising prospects for the future treatment of TNBC.

3 THE MONOTHERAPY OF IMMUNE-CHECKPOINT INHIBITORS

3.1 Anti-CTLA-4 Therapy

CTLA-4 sends inhibitory signals to active T cells and conflicts with CD28 for attaching to B7. This action impacts CD4+ T cell cloned proliferation and trafficking, inhibits the T cell cycle's advancement, and lowers IL-2 production. (Liu et al. 2023). CTLA-4 inhibitors work by preventing the interaction between CTLA-4 and B7 on the membranes of antigen-presenting cells (APCs). This is the major mechanism by which they influence the immune system. Thus, they enhance the activation of T cells and multiplication and enable T cells to perform their regular immunological tasks by blocking inhibitory signals (Sutanto et al. 2024). Additionally, CTLA-4 inhibitors can promote the depletion of regulatory T cells (Tregs), which maintain immune tolerance in the tumor microenvironment. This depletion enhances anti-tumor capabilities (Sutanto et al. 2024). In bladder cancer (BC), CTLA-4 mAbs can also directly kill CTLA-4+ BC cells by inducing antibody-dependent cellular cytotoxicity (ADCC) mediated by tumor-associated macrophages (Zhang et al. 2023).

The CTLA-4 inhibitors most frequently approved for therapeutic purposes are ipilimumab and tremelimumab. First investigated in metastatic melanoma, ipilimumab is a human immunoglobulin IgG1 mAb that interacts to CTLA-4. It is currently being evaluated for safety in early-stage breast cancer patients in the Phase I clinical trial NCT01502592. Tremelimumab is a human immunoglobulin IgG2 mAb targeting CTLA-4. The Phase II clinical trial NCT02527434 assessed the efficacy of tremelimumab in TNBC and other cancers, demonstrating that tremelimumab is a viable treatment option for TNBC (Zhang et al. 2023). According to studies, TNBC has high levels of CTLA-4 expression, which promotes tumor immune evasion (Ji et al. 2023). Consequently, this strategy still has a lot of potential for growth in the immunotherapy of TNBC, even though there aren't any medicines approved by the FDA for anti-CTLA-4 therapy in TNBC at the moment.

3.2 Anti-PD-1/PD-L1 Therapy

The PD-1 receptor is a member of the CD28 superfamily. It attracts the intracellular phosphatases when it connects to its ligand PD-L1. Through a series of events, these phosphatases disable subsequent effectors of stimulation of T cells, which eventually results in the death of T cells or apoptosis (Bullock & Richmond 2024). The connection between PD-1 and PD-L1 delivers inhibitory signals to T cells, hindering their activation and enabling cancer cells to evade immune system identification. The basis of the inhibitor technique is the use of mAbs or tiny chemicals to prohibit PD-1 from conforming to PD-L1/2. This blockage revitalizes the immunological activity within the tumor microenvironment (TME) and returns T cells to their cytotoxic function (Wen et al. 2024).

In BC, both PD-1 and PD-L1 may function as targets for ICIs, with PD-L1 being particularly notable due to its high expression in TNBC. The FDA has currently allowed a number of mAbs that target PD-1/PD-L1, including durvalumab, avelumab, pembrolizumab, atezolizumab, cemiplimab, and nivolumab (Liu et al. 2023). For the treatment of TNBC, research has primarily focused on pembrolizumab and atezolizumab. Based on the findings of the KEYNOTE-522 study, the FDA has authorized KEYTRUDA (pembrolizumab) in order to cure of high-risk early-stage TNBC. It is used as a single-agent adjuvant medication after surgery (Tarantino et al. 2022). The FDA previously granted rapid clearance for the anti-PD-L1 mAb atezolizumab for PD-L1-positive, unresectable locally advanced TNBC or mTNBC. But after the follow-up confirmatory stage III

Impassion131 trial failed to show benefits in OS or progression-free survival (PFS) when atezolizumab and paclitaxel were coupled as opposed to paclitaxel alone, this approval was revoked (Wen et al. 2024). Even though the FDA has only licensed a small number of PD-1 or PD-L1 single-agent treatments for the manegement of TNBC, PD-1/PD-L1 inhibitors remain to show great promise in managing TNBC.

4 COMBINATION TREATMENT

4.1 Antibody-Chemotherapy Combination Treatment

For many years, the standard treatment for TNBC has been chemotherapy following surgery. Conventional chemotherapeutic regimens usually consist of taxanes (AC-T) after cyclophosphamide and anthracycline (Leon-Ferre & Goetz 2023). Additionally, given that most TNBC patients harbor *BRCA* gene mutations, chemotherapy made up of platinum has been used to target DNA damage (He et al. 2021). The introduction of ICIs targeting PD-1/PD-L1 has led to their use in clinical practice. However, due to the inherent heterogeneity of TNBC, most patients show limited response to chemotherapy and ICIs monotherapy in clinical settings (Li et al. 2022).

With the advancement of ICIs treatment, combination therapies involving ICIs and chemotherapy have demonstrated superior outcomes in clinical trials. The clinical effectiveness and safety of platinum-based chemotherapy and ICIs in combination with chemotherapy for the initial stages TNBC were indirectly compared in a meta-analysis. The findings showed that, in comparison to platinum-based chemotherapy, the use of ICIs in conjunction with chemotherapy considerably increased the pathological complete response (pCR) rate and decreased adverse effects (AEs) in 1647 patients (He et al. 2021). mTNBC is often treated with monotherapy, but combination therapy can increase the objective response rate (ORR) from 10-30% to 63% (Liu et al. 2023). Patients who were selected at random to receive both pembrolizumab and chemotherapy during the KEYNOTE-522 experiment showed a noticeably higher pCR rate. Due to this discovery, the FDA authorized pembrolizumab with chemotherapy as neoadjuvant therapy for extremely dangerous, initial stages TNBC. Following surgery, the patients remained to receive monotherapy as an adjuvant treatment (Tarantino et al. 2022). The effectiveness of nab-paclitaxel monotherapy and atezolizumab in combination was evaluated in the IMpassion130 study. Patients suffering from advanced TNBC treated with combination therapy had a better prognosis than those treated with monotherapy, as evidenced by the longer median PFS and OS (Liu et al. 2023). Chemotherapy plus ICIs is more effective than chemotherapy alone for patients with advanced TNBC who express PD-L1 (CPS ≥10), according to a comparison of median OS between pembrolizumab and chemotherapy and placebo and chemotherapy in a trial evaluating the treatment of advanced TNBC. (Liu et al. 2023). Irrespective of PD-L1 expression conditions, the IMpassion031 study showed that atezolizumab plus neoadjuvant chemotherapy (NACT) enhanced pCR in the initial TNBC patients (Jin et al. 2024).

4.2 Combination of Immune Checkpoint Inhibitor Therapies

Combining therapy is a viable option for TNBC patients who do not react to immunochemotherapy since dual checkpoint (CTLA-4 and PD-1/PD-L1) inhibitors incorporate the benefits of both monotherapies. The synergistic advantages of this combined treatment include CTLA-4 mAbs blocking inhibitory second signals to promote the stimulation of T cells and reproduction., as well as PD-1/PD-L1 mAbs blocking their binding to enhance immune activity within the TME (Li et al. 2021). In a study using a mouse model of TNBC, the effects of combining antibodies were assessed. The outcomes demonstrated that combination therapy was more effective than monotherapy at inhibiting tumor growth. According to another research, CTLA-4 and PD-1 mAbs dramatically inhibit tumour growth and dissemination by augmenting T cell infiltration inside BCs (Zhang et al. 2023). Multiple preclinical models have demonstrated that the concurrent use of CTLA-4 and PD-1 mAbs enhances the inhibitory effect on tumors compared to monotherapy, indicating that combination therapy can compensate for the limitations of single-agent treatment (Geurts & Kok 2023). Clinical studies have assessed the combined treatment of drugs that block the PD-1/PD-L1 and CTLA-4 for a number of BC types, including as metastatic HER2-negative breast cancer, metaplastic breast cancer (MpBC), and TNBC. A discontinued stage two clinical study (NCT03982173) for TNBC examined the combination of the CTLA-4 inhibitor

tremelimumab and the PD-L1 inhibitor durvalumab (Zhang et al. 2023).

5 IMMUNE-RELATED ADVERSE EVENTS

The therapeutic management of TNBC has advanced significantly thanks to ICIs, both alone and in combination. However, TNBC remains a disease with a poor prognosis and is often associated with immune-related adverse events (irAEs). IrAEs happen when the patient's healthy cells are erroneously attacked by the immune system, which is completely engaged by immunotherapy. This can result in a variety of adverse events (Wen et al. 2024). Anemia, diarrhea, limb pain, and trouble breathing are the most frequent irAEs observed in clinical studies using CTLA-4 inhibitors only for BC. In severe cases, fatal complications such as myasthenia gravis and uremia have been reported (Zhang et al. 2023). According to a meta-analysis, gastrointestinal, dermatological, thoracic, and respiratory adverse events (DAEs) are often linked to ICIs blockers. The incidence of irAEs is also related to gender and age. In KEYNOTE-522 clinical study for TNBC treatment, the most common irAEs during the combination therapy phase of ICIs and chemotherapy were infusion reactions, thyroid dysfunction, skin toxicity, and pneumonia. Some of these damages are irreversible and may potentially affect fertility in premenopausal patients (Tarantino et al. 2022). Therefore, the irAEs brought about by ICIs treatment should not be overlooked, and future efforts should focus on improving drugs to reduce the impact of irAEs on patients. In clinical practice, to facilitate the proper development of tumor immunotherapy treatment plans and intervention strategies, physicians need to continuously monitor patients for symptoms of irAEs and conduct systematic research on irAEs (Zhang et al. 2023).

6 CONCLUSION

Substantial improvements have been achieved with the remedy of BC during the course of the previous several years thanks to the use of ICIs. As a subtype of invasive BC, TNBC has long lacked targeted therapies. However, immunotherapy has become a viable therapeutic option as our understanding of the molecular and immunological features of TNBC has grown. The TME, tumor vaccines, immunotherapy, integrated traditional Chinese and Western medicine therapies, and innovative medicines such cell cycle inhibitors and DNA damage response inhibitors are the main areas of current research on TNBC therapeutics. CTLA-4 inhibitors have been widely used in solid tumors such as metastatic melanoma, but there are currently no FDA-approved immunotherapies specifically for TNBC. TNBC cancer cells frequently overexpress PD-1/PD-L1, which makes it a more researched target for immunotherapy. Currently, the FDA has authorised the utilisation of the PD-1 inhibitor pembrolizumab plus chemotherapy for clinical management of TNBC patients. This combination therapy overcomes the limitations of ICIs or chemotherapy alone and has improved clinical response rates. However, studies have shown that TNBC patients generally do not respond well to ICIs monotherapy.

The research is ongoing for combination therapies involving ICIs with chemotherapy, radiotherapy, gene therapy, nanotechnology, and dual checkpoint inhibitors, offering hope for more effective TNBC treatments in the future. The combined effort of immunotherapy and chemotherapy is regarded as the most successful medication for TNBC; nonetheless, it is linked to increased immunotoxicity compared to chemotherapy alone and may induce numerous irAEs.Treating TNBC remains a significant challenge. Future research on ICIs combination therapies will need to focus on addressing immune deficiencies and side effects to minimize the harm of drugs to patients. Additionally, exploring more immunosuppressive targets, new biomarkers, and novel drugs is expected to improve the cure rate and prognosis for TNBC.

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