Review Article

Narrative review on advancing breast cancer treatment: harnessing the power of PD-1/PD-L1 inhibitors for improved patient outcomes

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Background and Objective: Cancer immunotherapy has significantly advanced the field of oncology, providing novel therapeutic strategies for various malignancies, including breast cancer. The programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) pathway is pivotal in immune regulation, and its inhibitors have demonstrated therapeutic benefits in diverse tumors. This review aims to critically examine the role, clinical efficacy, safety, and future directions of PD-1/PD-L1 inhibitors in breast cancer treatment, with a focus on pembrolizumab, nivolumab, and tislelizumab, and to elucidate the challenges and prospects in this dynamic field.

Methods: A comprehensive literature search was conducted, adhering to Narrative Review reporting checklist for transparent reporting. Data from selected studies were qualitatively analyzed to synthesize key findings related to the mechanisms of action, clinical applications, and challenges of PD-1/PD-L1 inhibitors in breast cancer.

Key Content and Findings: PD-1 inhibitors have shown remarkable efficacy in various malignancies, including advanced triple-negative breast cancer (TNBC), where they have been investigated both in combination with chemotherapy and as neoadjuvant/adjuvant treatment. The exploration of these inhibitors in other breast cancer subtypes, such as human epidermal growth factor receptor-positive and hormone receptor-positive breast cancer, is ongoing. The review highlights the challenges in patient selection, management of immune-related adverse events (irAEs), and the emergence of resistance mechanisms. It underscores the need for ongoing research focusing on identifying reliable predictive biomarkers, elucidating mechanisms of resistance, and optimizing treatment strategies.

Conclusions: PD-1/PD-L1 inhibitors hold substantial promise in advancing breast cancer treatment. This review provides critical insights and emphasizes the clinical importance of continued scientific exploration to refine patient selection criteria, improve treatment outcomes, and expand the applications of immunotherapy in breast cancer. Further research is imperative to overcome the existing challenges and realize the full therapeutic potential of these inhibitors in breast cancer and other malignancies.

Keywords: Breast cancer; immunotherapy; pembrolizumab; immune checkpoint inhibitors (ICIs)

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Introduction

Background

Breast cancer stands as one of the most prevalent malignancies, affecting a significant portion of the global population. The current treatment modalities for breast cancer encompass a range of strategies, including surgery, chemotherapy, radiation therapy, hormonal therapy, and targeted therapy, each tailored to the patient's specific type and stage of cancer (1). Amidst these, cancer immunotherapy has burgeoned as a pivotal approach, particularly in addressing the limitations and challenges posed by conventional treatments.

In the realm of cancer immunotherapy, the programmed cell death protein 1/programmed cell death-ligand 1 (PD-1/PD-L1) pathway has been spotlighted due to its crucial role in modulating immune responses within the tumor microenvironment (TME). The interaction between PD-1, a receptor expressed on activated T cells, and PD-L1, often upregulated in tumor and immune cells, results in T-cell exhaustion and enables tumor cells to evade immune surveillance (2). This understanding has paved the way for the development of PD-1/PD-L1 inhibitors, which aim to block this interaction and reinvigorate anti-tumor immune responses.

Pembrolizumab, as a representative of PD-1 inhibitors, has demonstrated substantial efficacy across various malignancies, including melanoma, non-small cell lung cancer (NSCLC), bladder cancer, and notably, breast cancer (3). Within the context of breast cancer, pembrolizumab, alongside other PD-1 inhibitors like nivolumab and tislelizumab, has been subjected to rigorous investigation to enhance patient outcomes. Notably, on July 26, 2021, the Food and Drug Administration (FDA) approved pembrolizumab in combination with chemotherapy as a neoadjuvant treatment for high-risk, early-stage triple-negative breast cancer (eTNBC), followed by its continued use as a single agent as adjuvant treatment post-surgery (4).

Rationale and knowledge gap

Despite the promising strides made with pembrolizumab, particularly in treating advanced TNBC, the exploration of PD-1/PD-L1 inhibitors in other breast cancer subtypes, such as human epidermal growth factor receptor-positive and hormone receptor-positive breast cancer, remains an active research frontier. Preliminary evidence hints at the potential for broader applications of immune checkpoint inhibitors (ICIs) across these subtypes (5). However, challenges persist, such as patient selection, management of immune-related adverse events (irAEs), and resistance mechanisms, which necessitate ongoing investigation and research endeavors.

Objective

This review seeks to delve into the burgeoning field of PD-1/PD-L1 inhibitors in breast cancer treatment, with a particular focus on TNBC. The regulatory approval of pembrolizumab underscores a significant milestone in immunotherapy, prompting continued research efforts aimed at refining patient selection criteria, enhancing treatment outcomes, and broadening the application of immunotherapy in breast cancer. Through a comprehensive lens, this review endeavors to provide critical insights into the current state of PD-1/PD-L1 inhibitors in breast cancer treatment and underscores the imperative for further scientific exploration in this dynamic field. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-23/rc).

Methods

Literature search strategy

A comprehensive literature search was conducted to identify relevant articles and studies related to the role of PD-1/PD-L1 inhibitors in breast cancer treatment. Electronic databases, including PubMed, Google Scholar, Clinicaltrials.gov, were systematically searched using appropriate keywords and MeSH terms. The search was restricted to open-access articles published in *PLOS Medicine* and other reputable scientific journals.

For eligibility, our concentration was directed towards phase I–III trials examining TNBC patients undergoing neoadjuvant treatment, specifically involving the utilization of ICIs in conjunction with chemotherapy. Additionally, when accessible, we took into consideration trials that presented distinct results for molecularly defined subgroups within breast cancer subtypes, excluding TNBC (*Table 1*).

Study selection

Articles were screened based on predefined inclusion and exclusion criteria. Studies included in this review were

Table 1 The search strategy summary

Items	Specification
Date of search	1 March 2023 to 1 May 2023
Databases and other sources searched	PubMed, Google Scholar, Clinicaltrials.gov
Search terms used	"Early-stage triple negative breast cancer" OR "early-stage TNBC" OR "eTNBC" [MeSH]; ("Early-stage TNBC") AND "recurrence and mortality" [MeSH]; ("Early-stage TNBC") AND "prognosis" [MeSH]; "Immunotherapy" OR "Immune checkpoint inhibitors" OR "Pembrolizumab" OR "Atezolizumab" OR "Durvalumab" [MeSH]; "Neoadjuvant" [MeSH]; "Adjuvant" [MeSH]; "Monotherapy" [MeSH]; "Combination therapy" [MeSH]; ("Early-stage TNBC") AND "predict" OR "forecast") [MeSH]; "Early-stage TNBC" AND "endpoint" [MeSH]; "Early-stage TNBC" AND "efficacy" [MeSH]; "PD-L1" [MeSH]; "TIL" [MeSH]; "TMB" [MeSH]
Timeframe	2010–2023
Inclusion and exclusion criteria	Inclusion criteria: the scope of our selection encompasses research articles, reviews, and clinical trials articulated in English, with a thematic focus on early-stage triple-negative breast cancer and immunotherapy. Exclusion criteria: certain papers were omitted from consideration due to perceived low reliability
Selection process	The included literature was selected by author Fan Zhang, reviewed by both authors
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

required to be original research articles, clinical trials, or systematic reviews/meta-analyses that investigated the efficacy, safety, and mechanisms of action of PD-1/PD-L1 inhibitors in breast cancer. Only articles published in the English language were considered. Studies focusing on other cancer types or non-PD-1/PD-L1-related immunotherapies were excluded.

Data extraction and analysis

Data from the selected studies were extracted using a standardized data extraction form. The following information was collected: study characteristics (author, year, study design), patient population (sample size, age, tumor subtype), intervention details (type of PD-1/PD-L1 inhibitor, treatment regimen), outcomes assessed (efficacy, safety), and key findings.

The extracted data were analyzed qualitatively to provide a comprehensive overview of the role of PD-1/PD-L1 inhibitors in breast cancer treatment. The efficacy outcomes, including overall response rate, progression-free survival (PFS), and overall survival (OS), were summarized. Safety data, including the incidence and type of irAEs, were also reported.

Quality assessment

The quality and risk of bias of the included studies were assessed using appropriate tools, such as the Cochrane Collaboration's tool for assessing the risk of bias in randomized controlled trials or the Newcastle-Ottawa Scale for non-randomized studies. The quality assessment helped ensure the reliability and validity of the included studies.

Data synthesis

The findings from the included studies were synthesized and presented in a descriptive manner. Where applicable, quantitative data were summarized using appropriate statistical measures, such as mean, median, or proportions. Any discrepancies or conflicting findings among the studies were noted and discussed.

Limitations

The limitations of this review include the reliance on published literature, which may introduce publication bias, and the exclusion of non-English articles, which could lead

to language bias. Additionally, the interpretation of the data is limited by the inherent variations in study design, patient populations, and treatment regimens across the included studies.

Results

PD-1/PD-L1 inhibitors in breast cancer

Use of PD-1/PD-L1 inhibitors in later-stage breast cancer

Rationale for using immunotherapy in advanced breast cancer

The rationale for using immunotherapy in advanced breast cancer is based on the understanding of breast cancer's immunogenicity and the potential of immunotherapeutic strategies to enhance the host immune response against cancer cells.

Breast cancer has traditionally been considered poorly immunogenic, but recent advancements in immunobiology have demonstrated the presence of immune-related factors and immune cell subsets in the TME that contribute to the anti-tumor immune response (6). Tumor-infiltrating lymphocytes (TILs) and immune gene signatures have been associated with a favorable clinical outcome in breast cancer, particularly in TNBC and HER2-positive breast cancer. These findings have prompted investigations into immunotherapeutic strategies for breast cancer treatment.

In advanced breast cancer, particularly in TNBC, the combination of immunotherapy based on PD-1/PD-L1 inhibitors with chemotherapy has shown effectiveness in phase 3 clinical trials. These positive results have led to the approval of ICIs for TNBC, providing new therapeutic possibilities for aggressive tumors and hard-to-treat populations.

Clinical trials and findings

(I) PD-1 inhibitors

The clinical trial NCT01848834, also known as the KEYNOTE-012 study, assessed the effectiveness and safety of pembrolizumab, an ICI targeting PD-1, in patients with advanced TNBC (7). This phase Ib, multicenter, nonrandomized trial included 111 TNBC patients screened for PD-L1 expression, with 58.6% having PD-L1-positive tumors. Thirty-two women with advanced PD-L1-positive TNBC received intravenous pembrolizumab at 10 mg/kg every 2 weeks, with a median of five doses administered. Results showed promising antitumor activity, with an 18.5% overall response rate among 27 evaluable patients. The median time to response was 17.9 weeks, and the median duration of response (DOR) was not yet reached. Pembrolizumab demonstrated an acceptable safety profile, with mild common toxicities like arthralgia, fatigue, myalgia, and nausea. Grade ≥3 toxicity was observed in 15.6% of patients, and one treatment-related death was reported. In conclusion, the phase Ib KEYNOTE-012 study provided preliminary evidence of pembrolizumab's clinical activity and safety in heavily treated, advanced TNBC. Immune checkpoint inhibition with pembrolizumab appears promising for this challenging breast cancer type. Ongoing investigations include a phase II study of pembrolizumab given once every 3 weeks at a 200-mg dose.

The results of the trial NCT02404441 showed that PDR001, an anti-PD-1 antibody, was evaluated as a single agent in adult patients with advanced solid tumors. The study consisted of a phase I dose escalation part and a phase II part. The primary outcome measures included determining the recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) for PDR001 in phase I and assessing the overall response rate (ORR) in phase II based on RECIST v1.1. In the phase I part, the exposure [area under the curve (AUC)] after the first dose of treatment at cycle 3 was estimated to determine the RP2D and MTD for PDR001. Additionally, the incidence of dose-limiting toxicities (DLTs) was evaluated. In the phase II part, the ORR was assessed based on the best overall response of complete response (CR) or partial response (PR) as per RECIST v1.1. The study enrolled a total of 319 participants with various solid tumor types, including melanoma, NSCLC, TNBC, anaplastic thyroid cancer, and others. The trial commenced on April 27, 2015, and the actual study completion date was July 21, 2020. Overall, the trial aimed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of PDR001 in patients with advanced malignancies, providing valuable information about its efficacy in treating solid tumors.

The clinical trial NCT02657889, also known as TOPACIO/Keynote-162, is a phase 1/2 study that investigated the combination of niraparib, an oral PARP inhibitor, and pembrolizumab, an anti-PD-1 monoclonal antibody, in patients with advanced TNBC or recurrent ovarian cancer (ROC). Eligible patients had to demonstrate a response lasting at least 6 months to first-line platinum therapy and were considered to have platinum-resistant ovarian cancer (PROC) based on investigator assessment. The study established the RP2D of niraparib at 200 mg orally once daily and pembrolizumab at 200 mg IV every

21 days. As of January 2018, 62 patients were enrolled, and 60 of them were evaluable for response assessment. The ORR, which includes CR and PR, was 25% in all PROC patients and 45% in patients with tumor BRCA (tBRCA) mutations. The disease control rate (DCR), including CR, PR, and stable disease (SD), was 68% in all PROC patients and 73% in tBRCA mutation (tBRCAmut) patients. The combination of niraparib and pembrolizumab showed promising efficacy, particularly in patients with tBRCAmuts. Responses were observed in patients with PROC, primary platinum-refractory disease, and platinum-sensitive disease. The durability of response data was still being assessed at the time of the study. The most common grade ≥3 treatment-emergent adverse events (TEAEs) were anemia (19%) and thrombocytopenia (9%), and no new safety signals were identified with the combination treatment. In conclusion, the combination of niraparib and pembrolizumab demonstrated favorable response rates and appeared to be a promising treatment option for patients with advanced TNBC and ROC. Further evaluation of this combination in ROC is warranted.

NCT03789110 is a phase II clinical trial investigating the combination of nivolumab (an anti-PD-1 checkpoint inhibitor) and ipilimumab [an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibody] for the treatment of metastatic hypermutated HER2-negative breast cancer. Phase II trials assess the safety and effectiveness of an investigational drug to determine if it works against a specific disease. Nivolumab is designed to enable the body's immune system to target and destroy tumors, while ipilimumab works to prevent the immune system from suppressing its ability to fight this specific type of cancer. Although both nivolumab and ipilimumab have been approved by the U.S. FDA for other uses like melanoma and renal cell carcinoma, they have not yet been approved for this specific disease (metastatic hypermutated HER2-negative breast cancer) when used in combination. The primary objective of this trial is to assess the efficacy of nivolumab and ipilimumab in treating breast cancer that has spread to other parts of the body. Additionally, researchers are investigating specific DNA or protein markers in the blood or tumor tissue that may indicate the potential effectiveness of this combination treatment in future patients. It's important to note that the combination of nivolumab and ipilimumab is not yet FDA-approved for this specific type of breast cancer, and this study aims to determine its safety and effectiveness.

NCT03184558 is a phase II clinical trial investigating the combination of bemcentinib (BGB324), a selective Axl kinase inhibitor, with pembrolizumab, a PD-1 inhibitor, for the treatment of previously treated, locally advanced and unresectable, or metastatic TNBC or triple negative inflammatory breast cancer (TN-IBC). The study is open-label, single-arm, and multi-center, aiming to assess the anti-tumor activity and safety of the combination. The primary objective of the trial is to evaluate the ORR in participants receiving bemcentinib + pembrolizumab. Secondary outcome measures include DOR, DCR, PFS, and OS. The trial started on July 26, 2017, and completed on August 20, 2018. It enrolled 29 participants with locally advanced and unresectable, or metastatic TNBC or TN-IBC. Eligible patients had received one or more prior therapies for TNBC or inflammatory breast cancer in the metastatic setting, and prior treatment must have included a prior taxane and/or anthracycline-based therapy.

The clinical trial NCT02819518, known as the KEYNOTE-355 study, assessed the efficacy and safety of pembrolizumab, an ICI, combined with chemotherapy for previously untreated locally recurrent inoperable or metastatic TNBC (8). The phase III trial included 882 TNBC patients, divided into two parts. Part 1 evaluated pembrolizumab's safety with different chemotherapies, while Part 2 assessed pembrolizumab plus chemotherapy versus placebo plus chemotherapy for safety and efficacy. In Part 2, primary endpoints were PFS and OS in patients with PD-L1 combined positive score (CPS) ≥10 and ≥1 tumors, and all participants. Pembrolizumab combined with chemotherapy significantly improved PFS in patients with CPS ≥10 tumors compared to chemotherapy alone. Although the OS boundary for significance in CPS ≥1 tumors wasn't met, the treatment effect increased with PD-L1 enrichment. Overall, pembrolizumab plus chemotherapy led to a statistically significant and clinically meaningful improvement in OS for patients with previously untreated locally recurrent inoperable or metastatic TNBC expressing PD-L1 (CPS ≥10). The combination was well-tolerated, with no new safety concerns. These findings suggest that pembrolizumab combined with chemotherapy holds promise as a therapeutic approach for certain patients with metastatic TNBC. Ongoing investigations and follow-up studies aim to explore its potential as a treatment option for this challenging breast cancer type.

The HARMONIA trial compared ribociclib and palbociclib in patients with advanced breast cancer within the HER2-enriched intrinsic subtype (9). The trial included an exploratory cohort treated with paclitaxel

+/– tislelizumab. The primary objective was to assess if ribociclib combined with endocrine therapy was superior to palbociclib in prolonging PFS in patients with HR+/HER2– and HER2-E breast cancer. The study enrolled patients with HER2-E disease from multiple sites worldwide. The main cohort was randomly assigned to receive either ribociclib or palbociclib with endocrine therapy. The key secondary endpoint was OS, and ribociclib demonstrated a significant OS benefit compared to placebo. The findings suggest ribociclib's potential as an effective treatment option for HR-positive, HER2-negative advanced breast cancer, including the HER2-E subtype.

NCT05760378 is a phase III clinical trial conducted to assess the efficacy and safety of famitinib in combination with camrelizumab plus treatment of physician's choice (TPC) compared to camrelizumab plus TPC alone in the first-line treatment of immunomodulatory locally advanced or metastatic TNBC. The trial is open-label and randomized, with an estimated enrollment of 223 participants. The primary outcome measure is PFS, while secondary outcome measures include ORR, DOR, clinical benefit rate (CBR), and OS. Patients eligible for the study must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1 and histologically documented TNBC (absence of HER2, ER, and PR expression). They should have not received previous chemotherapy or targeted therapy for metastatic TNBC. The trial started on March 17, 2023, and its estimated primary completion date is January 1, 2025.

(II) PD-L1 inhibitors

The clinical trial NCT04296942, titled "BN-Brachyury, Entinostat, Adotrastuzumab Emtansine and M7824 in Advanced Stage Breast Cancer (BrEAsT)", aims to investigate a new combination of immunotherapy drugs for the treatment of metastatic breast cancer, including TNBC and HER2+ breast cancer (10). Adults aged 18 and older with metastatic breast cancer are eligible to participate. Participants will be assigned to one of three groups, receiving different drugs based on their group. The treatment includes Bavarian Nordic (BN)-Brachyury, M7824 (Bintrafusp alfa), and ado-trastuzumab emtansine (T-DM1) or Kadcyla, along with Entinostat for some participants. The study will assess tumor response by conducting various tests, including tumor scans (computed tomography, magnetic resonance imaging, and/or bone scan), blood and urine tests, and clinical exams. Participants will be monitored during the study and undergo scans every 6 weeks to evaluate treatment efficacy. Treatment will continue until disease progression, development of side effects, or patient preference to stop. Follow-up visits or telephone calls will be conducted approximately 28 days after treatment completion, with subsequent contacts every 3 months for 1 year, then every 6 months for an additional year.

In the clinical trial with the identifier NCT03330405, the results showed that the combination of avelumab and talazoparib in locally advanced or metastatic solid tumors was generally well-tolerated (11). The study assessed the number of participants with TEAEs, grade ≥3 TEAEs, serious TEAEs, TEAEs leading to discontinuation of any study drug, TEAEs leading to discontinuation of all study drugs, and TEAEs leading to death. Additionally, PK data of serum avelumab concentrations and predose/postdose plasma talazoparib concentrations were analyzed. Immunogenicity blood samples were also tested for anti-drug antibodies. However, the specific efficacy outcomes and overall treatment response were not summarized in the provided information.

Use of PD-1/PD-L1 inhibitors in early-stage breast cancer

Benefits and potential limitations

(I) Benefits

PD-1/PD-L1 inhibitors have shown several benefits when used in early-stage breast cancer, including enhanced immune response, improved pathological response, and tailored therapy. Here's a comprehensive reply to each of these views:

Enhanced immune response: PD-1/PD-L1 inhibitors enhance the immune response in early-stage breast cancer by blocking the interaction between the PD-1 receptor on immune cells and PD-L1 on tumor cells. This interaction inhibits the immune response and allows tumor cells to evade immune surveillance. By blocking this interaction, PD-1/PD-L1 inhibitors restore the function of immune cells, particularly T cells, and enhance their ability to recognize and target tumor cells. This leads to an increased immune response against the tumor, potentially resulting in improved outcomes for patients.

Improved pathological response: PD-1/PD-L1 inhibitors have been associated with improved pathological response in early-stage breast cancer. Pathological response refers to the extent of tumor regression or eradication observed after treatment. Studies have shown that PD-1/PD-L1 inhibitors, when used as neoadjuvant therapy (given before surgery), can lead to a higher rate of complete or partial pathological

response compared to standard treatments alone. This indicates that PD-1/PD-L1 inhibitors can effectively shrink or eliminate tumors, potentially improving the chances of successful surgical removal and reducing the risk of disease recurrence.

(II) Limitations

Limitations of using PD-1/PD-L1 inhibitors in early-stage breast cancer can be viewed from the perspectives of patient selection, adverse effects, and resistance/non-responsiveness. Here are the limitations:

- Patient selection: PD-1/PD-L1 inhibitors may have limitations in terms of patient selection for early-stage breast cancer. Currently, these inhibitors are primarily approved for use in advanced or metastatic cancers. Limited clinical evidence exists to support their use as a standard treatment option in early-stage breast cancer. More research is needed to determine the specific patient subgroups that would benefit the most from PD-1/PD-L1 inhibitors in the early-stage setting.
- Adverse effects: the use of PD-1/PD-L1 inhibitors is associated with irAEs. While the incidence of irAEs is generally lower with PD-1/PD-L1 inhibitors compared to CTLA-4 blockade, they can still occur. Adverse effects can include fatigue, rash, diarrhea, pneumonitis, and endocrine dysfunction, among others. Early-stage breast cancer patients may have a lower tolerance for these adverse effects, and the potential benefits of PD-1/PD-L1 inhibitors should be carefully weighed against the risks.
- Resistance and non-responsiveness: another limitation is the development of resistance or non-responsiveness to PD-1/PD-L1 inhibitors. While these inhibitors have shown efficacy in a subset of patients, a significant proportion of patients may not respond or may develop resistance over time. The mechanisms underlying resistance to PD-1/PD-L1 inhibitors are complex and not yet fully understood. Tumor heterogeneity, alterations in tumor antigen presentation, and immune escape mechanisms can contribute to resistance. Identifying predictive biomarkers and understanding the factors that influence responsiveness to PD-1/PD-L1 inhibitors in early-stage breast cancer is an ongoing area of research.

Clinical trials and finding

The clinical trial NCT03197389 consists of two parts: a retrospective study and a prospective clinical study using pembrolizumab (Keytruda®, Dublin, Ireland) for early breast cancer (phase 0). The retrospective study (S58910) aims to analyze the expression of PD-L1 in ER/PR negative breast tumors and correlate it with TILs, proliferation, apoptosis expression, and clinical outcome (development of distant metastases). The phase 0 study is a single-center, open-label, non-randomized trial involving patients with early breast cancer. Participants will receive one intravenous injection of pembrolizumab (Keytruda®) at 200 mg approximately 10±4 days before surgery. The phase 0 study includes two cohorts: cohort A for patients scheduled for upfront surgery (with subcohorts for Her2 negative, Her2 positive, and ER positive tumors) and cohort B for patients who received neoadjuvant chemotherapy and still have residual tumor on imaging (with subcohorts for Her2 negative, Her2 positive, and ER positive tumors). Adverse experiences/events will be monitored and evaluated based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The objective is to assess the effect of pembrolizumab on biomarkers in early breast cancer patients, specifically evaluating PD-L1 expression and its correlation with clinical outcomes.

The use of PD-1/PD-L1 inhibitors in early-stage breast cancer has been an area of active research and exploration. While breast cancer has traditionally been considered less immunogenic compared to other solid tumors, combination therapies have shown potential in improving the immunogenicity of tumors and sensitizing breast cancer cells to immunotherapy.

The research article titled "Cost-Effectiveness of Neoadjuvant Pembrolizumab Plus Chemotherapy Followed by Adjuvant Single-Agent Pembrolizumab for High-Risk Early-Stage Triple-Negative Breast Cancer in the United States" (12) evaluates the cost-effectiveness of pembrolizumab in combination with chemotherapy as neoadjuvant treatment and continued as a single-agent adjuvant treatment after surgery for high-risk eTNBC in the United States. Based on their findings, the authors concluded that neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant single-agent pembrolizumab is considered a cost-effective option for high-risk eTNBC in the United States when compared to neoadjuvant chemotherapy alone.

A research article titled "Immunotherapy in breast cancer: an overview of current strategies and perspectives" (6) indicates that ICI have demonstrated efficacy in TNBC, leading to improved outcomes in terms of PFS and OS. Combination strategies involving ICIs and other targeted therapies, such as HER2-directed therapies, bispecific

antibodies, and adoptive cell transfer therapy, are being explored to enhance response rates and clinical outcomes. Neoadjuvant immunotherapy has shown positive results in TNBC, with higher rates of pathological CR (pCR). However, the use of immunotherapy in luminal and HER2-positive breast cancer is still under investigation. Challenges include managing immunotherapy-related adverse events and identifying predictive biomarkers for patient selection. Researchers are also exploring the development of cancer vaccines targeting HER2 and non-HER2 tumor-associated antigens (TAAs). Although therapeutic cancer vaccines have shown modest results, personalized neoantigen vaccines hold promise. Ongoing research aims to optimize the timing, combination strategies, and patient selection criteria to maximize the clinical benefit of immunotherapy in early breast cancer, especially TNBC. Further studies are needed to address the challenges associated with immunotherapy and determine its long-term impact on patient outcomes.

In conclusion, the use of PD-1/PD-L1 inhibitors in early-stage breast cancer, particularly in TNBC, has shown promising results and has the potential to revolutionize the treatment paradigm for breast cancer. Ongoing research and clinical trials continue to explore the efficacy and safety of PD-1/PD-L1 inhibitors in different subtypes and stages of breast cancer, aiming to improve patient outcomes and expand the application of immunotherapy in breast cancer treatment.

Features of pembrolizumab in breast cancer treatment

Pembrolizumab in eTNBC

In the neoadjuvant setting, Pembrolizumab has been studied in combination with chemotherapy as a treatment before surgery. The phase 3 clinical trial KEYNOTE-522 investigated the addition of pembrolizumab to neoadjuvant chemotherapy in patients with previously untreated stage II or stage III TNBC. The trial showed that the percentage of patients achieving a pCR was significantly higher in the pembrolizumab-chemotherapy group compared to the placebo-chemotherapy group (13). The pCR rate was 64.8% in the pembrolizumab-chemotherapy group and 51.2% in the placebo-chemotherapy group at the first interim analysis.

Immunotherapy, as a comprehensive treatment approach from neoadjuvant to adjuvant therapy, has demonstrated significant improvements in pCR rates in early-stage cancer. However, it's important to note that pCR is not the ultimate endpoint for early-stage tumors. Previous chemotherapy regimens do not always reflect the OS benefits. Therefore, early-stage treatment should not solely focus on achieving pCR.

Full-course immunotherapy for early-stage cancer has shown a notable enhancement in event-free survival (EFS), with the ultimate goal of improving long-term survival. The KEYNOTE-522 trial revealed not only the benefits of pCR but also improvements in EFS with the use of immunotherapy. Other early-stage studies exploring immunotherapy and its impact on EFS should also be considered to further elaborate on this matter.

Long OS with pembrolizumab

The clinical trial results confirm that pembrolizumab is a breakthrough treatment for TNBC, especially for patients with tumors expressing PD-L1 with a CPS of at least 10 (14). The combination of pembrolizumab and chemotherapy improved OS in this subgroup, compared to chemotherapy alone.

In the phase 3 KEYNOTE-355 trial, the addition of pembrolizumab to chemotherapy demonstrated longer OS in patients with advanced TNBC whose tumors expressed PD-L1 with a CPS of 10 or more (8). The trial included patients with previously untreated locally recurrent inoperable or metastatic TNBC. The results showed that in the CPS-10 subgroup, the median OS was 23.0 months in the pembrolizumab-chemotherapy group compared to 16.1 months in the placebo-chemotherapy group.

The other study, known as the KEYNOTE-522 trial, investigated pembrolizumab in the neoadjuvant setting for early TNBC. The trial included patients with previously untreated stage II or III TNBC. The addition of pembrolizumab to neoadjuvant chemotherapy showed a significantly higher percentage of patients achieving a pCR. However, the results regarding EFS have not been reported yet.

These findings highlight the potential of pembrolizumab in improving OS outcomes in advanced and early TNBC when used in combination with chemotherapy. However, it's important to note that these results are based on specific subgroups and further research is needed to explore its efficacy in broader patient populations.

Long OS of other ICIs

Nivolumab

A study published in *JAMA Oncology* (15) reported 5-year survival data for patients with advanced melanoma, renal cell carcinoma, or NSCLC treated with nivolumab. The study found that the 5-year survival rates ranged from 34%

to 44% across different cancer types.

Atezolizumab

Atezolizumab has demonstrated long-term survival benefits in certain cancers. In a clinical trial (16) for advanced bladder cancer, patients who received atezolizumab had a median OS of 15.9 months compared to 11.2 months with chemotherapy.

Durvalumab

In a clinical trial (17) for unresectable stage III NSCLC, durvalumab showed a significant improvement in OS compared to placebo. The 2-year OS rate with durvalumab was 66.3% compared to 55.6% with placebo.

Concise overview of the clinical distinctions between pembrolizumab and other PD-1/PD-L1 inhibitors in breast cancer treatment

Pembrolizumab, a PD-1 inhibitor, has demonstrated substantial efficacy in various cancers, notably NSCLC, by obstructing the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2, thereby enhancing the immune response against cancer cells. Distinguished from other inhibitors like nivolumab and atezolizumab by its specific targeting of PD-1, pembrolizumab has exhibited significant clinical efficacy, particularly in improving progression-free and OS in patients with PD-L1-positive advanced NSCLC. While generally more tolerable than chemotherapy, it's associated with fewer treatment-related and severe adverse events compared to platinum-based chemotherapy, albeit with potential for irAEs. Pembrolizumab has gained regulatory approvals for various cancers, including NSCLC and melanoma. In the realm of breast cancer, especially the advanced TNBC subtype, pembrolizumab has aligned with previous studies in showcasing potential to enhance treatment outcomes, warranting further detailed exploration by authors to substantiate its particular efficacy in breast cancer treatment.

Challenges and prospects of PD-1/PD-L1 therapy in breast cancer

Considerations for selecting the optimal PD-1/PD-L1 inhibitor

Patient-specific factors

(I) Overall health and performance status: the patient's overall health and performance status should be assessed to determine their ability to tolerate treatment and potential side effects.

(II) Age and comorbidities: age and the presence of other medical conditions (comorbidities) can influence treatment decisions and the selection of an appropriate PD-1/PD-L1 inhibitor.

(III) Tumor characteristics: tumor characteristics, including histology (type of cancer), PD-L1 expression levels, tumor mutational burden, and microsatellite instability, play a crucial role in determining the effectiveness of PD-1/PD-L1 inhibitors.

Comparative efficacy and side effect profiles:

(I) Clinical trial data: clinical trial data provides valuable information on the efficacy and safety profiles of different PD-1/PD-L1 inhibitors. Comparing data from various trials can help in making informed decisions.

(II) Response rates: response rates, such as CR, PR, stable disease, or progressive disease, indicate the effectiveness of a specific PD-1/PD-L1 inhibitor in treating a particular type of cancer.

(III) Side effect profiles: understanding the side effect profiles associated with different PD-1/PD-L1 inhibitors is crucial for selecting the optimal treatment. Side effects may vary among inhibitors and can impact a patient's quality of life.

(IV) FDA approvals: considering the approvals by the US FDA for specific indications can guide the selection of PD-1/PD-L1 inhibitors.

By taking into account patient-specific factors and evaluating the comparative efficacy and side effect profiles, healthcare professionals can make informed decisions to select the most suitable PD-1/PD-L1 inhibitor for individual patients. It's important to consider the latest research, clinical trial data, and FDA approvals to ensure optimal patient management and treatment outcomes.

Potential toxic side effects and irAEs

irAEs

PD-1/PD-L1 inhibitors can lead to irAEs, which occur due to the activation of the immune system. These adverse events can affect various organs and systems in the body.

Rash: PD-L1 inhibitors may be associated with a lower risk of any-grade rash compared to PD-1 inhibitors (18).

Elevated alanine aminotransferase: PD-L1 inhibitors may be associated with a lower risk of elevated alanine aminotransferase (a liver enzyme) compared to PD-1 inhibitors.

Colitis: PD-L1 inhibitors may be associated with a lower risk of colitis (inflammation of the colon) compared to PD-1 inhibitors.

Hypothyroidism: PD-L1 inhibitors may be associated

with a lower risk of hypothyroidism (underactive thyroid) compared to PD-1 inhibitors.

Other adverse events: while specific toxic side effects and irAEs can vary between individual PD-1 and PD-L1 inhibitors, the overall risk and profile of irAEs may differ. For example, different PD-1 or PD-L1 inhibitors may have varying risks of any-grade irAEs and grade ≥3 irAEs.

Predictive biomarkers and patient selection

PD-1/PD-L1 immunotherapy has shown promising results in the treatment of breast cancer. Several predictive biomarkers and factors can help determine the response to PD-1/PD-L1 blockade therapy. Here is a brief analysis:

Tumor mutation burden (TMB): TMB, which represents the number of somatic nonsynonymous mutations in cancer cells, has been identified as an important determinant of responsiveness to PD-1/PD-L1 immunotherapy. Higher TMB is associated with increased neoantigen expression, leading to enhanced immune recognition and response (19).

Genetic and epigenetic alterations: cancer cells can exploit their genetic and epigenetic aberrations to influence the immune landscape, leading to resistance to PD-1/PD-L1 therapy. Alterations in pathways such as MAPK/PTEN/PI3K, WNT/β-catenin, JAK/STAT, interferon-γ, and antigen processing/presentation pathways have been linked to resistance.

Immune microenvironment: the TME plays a crucial role in modulating the response to immunotherapy. Factors like T-regulatory cells, myeloid-derived suppressor cells, macrophages, and microbes within the TME can affect the response to PD-1/PD-L1 blockade.

To select patients for PD-1/PD-L1 immunotherapy, it is essential to evaluate these predictive biomarkers and factors. Assessing TMB, analyzing genetic and epigenetic alterations in cancer cells, and characterizing the immune microenvironment can provide valuable insights into patient selection. Additionally, omics-based approaches have been utilized to identify tumor intrinsic and extrinsic factors as potential predictive biomarkers.

Future research directions and possible improvements

PD-1/PD-L1 therapy has shown significant promise in the treatment of breast cancer, and future research directions and potential improvements can be explored. Here are some possible areas of focus: (I) combination therapies: investigating the potential of combining PD-1/PD-L1 inhibitors with other treatment modalities such as chemotherapy, targeted therapy, or other immunotherapies could enhance the therapeutic efficacy (20). Combinations with drugs targeting other immune checkpoints, such as CTLA-4 inhibitors, could also be explored to enhance the immune response against breast cancer. (II) Biomarker identification: identifying predictive biomarkers that can effectively stratify breast cancer patients who are more likely to respond to PD-1/PD-L1 inhibitors is crucial. This would help in selecting patients who are most likely to benefit from the therapy and avoid unnecessary side effects. Research efforts should focus on developing reliable biomarkers, such as PD-L1 expression levels, tumor mutational burden, immune cell infiltration, or specific genetic signatures (21). (III) Overcoming resistance: resistance to PD-1/PD-L1 therapy can occur in some patients. Understanding the mechanisms of resistance and developing strategies to overcome it is essential. Exploring combination approaches, targeting additional immune checkpoints, or modulating the TME to enhance T cell activity may help overcome resistance. (IV) Personalized treatment approaches: tailoring PD-1/PD-L1 therapy based on individual patient characteristics, such as tumor molecular subtypes or immune profiles, could improve treatment outcomes. Stratifying patients based on specific characteristics and optimizing treatment regimens accordingly may enhance the efficacy of PD-1/PD-L1 inhibitors in breast cancer. (V) Identifying and managing adverse events: PD-1/PD-L1 inhibitors can lead to irAEs. Future research should focus on better understanding and managing these adverse events to improve patient safety and treatment tolerability.

Discussion

The findings of this review are consistent with previous studies that have highlighted the significant breakthrough of PD-1/PD-L1 inhibitors in the field of breast cancer treatment. The PD-1/PD-L1 pathway, which plays a crucial role in immune regulation, has emerged as a target for immunotherapy in various malignancies, including breast cancer. The interaction between PD-1 and PD-L1 inhibits T-cell activity, allowing tumor cells to evade immune surveillance.

Clinical studies have demonstrated the therapeutic benefits of PD-1/PD-L1 blockade across multiple tumor types, leading to the approval of pembrolizumab, a PD-1 inhibitor, for the treatment of melanoma, NSCLC, bladder cancer, and several other malignancies. In breast cancer treatment, pembrolizumab has shown remarkable efficacy in advanced TNBC, both as a monotherapy and in

combination with chemotherapy.

The results of the KEYNOTE-012 trial, a phase 1b trial evaluating pembrolizumab in advanced PD-L1-positive TNBC, demonstrated an ORR of 18.5%, with durable responses observed. In the KEYNOTE-086 trial, pembrolizumab was assessed in patients with PD-L1-positive metastatic TNBC, showing an ORR of 21.4% and a median DOR of 10.1 months. These findings are consistent with previous studies reporting the efficacy of pembrolizumab in advanced TNBC.

Furthermore, the KEYNOTE-119 trial, a phase 3 trial investigating pembrolizumab versus chemotherapy in previously treated metastatic TNBC, showed a higher ORR of 23.1% with pembrolizumab compared to chemotherapy (11.6%) in the PD-L1-positive subgroup. These results suggest the potential of pembrolizumab in improving treatment outcomes for patients with PD-L1-positive TNBC.

Other PD-1/PD-L1 inhibitors, such as atezolizumab, have also shown efficacy in breast cancer treatment. The IMpassion130 trial, a phase 3 trial evaluating atezolizumab in combination with nab-paclitaxel in metastatic TNBC, demonstrated a significant improvement in PFS in the intent-to-treat population, particularly in the PD-L1-positive subgroup. Similarly, the IMpassion131 trial comparing atezolizumab plus paclitaxel to placebo plus paclitaxel in advanced TNBC showed potential benefits in PD-L1-positive patients.

The use of PD-1/PD-L1 inhibitors in early-stage breast cancer is an area of active research. While the efficacy of PD-1/PD-L1 inhibitors in TNBC has been established, their role in hormone receptor-positive and human epidermal growth factor receptor-positive breast cancer is still being investigated. Challenges in the implementation of PD-1/PD-L1 inhibitors in early-stage breast cancer include patient selection, management of irAEs, and the development of resistance or non-responsiveness to therapy.

Patient selection based on predictive biomarkers is crucial for optimizing the use of PD-1/PD-L1 inhibitors. TMB, genetic and epigenetic alterations, and the immune microenvironment have been identified as potential biomarkers for predicting responsiveness to PD-1/PD-L1 inhibitors. However, further research is needed to validate and refine these biomarkers.

The safety profile of PD-1/PD-L1 inhibitors is generally favorable compared to chemotherapy. While irAEs can occur, their incidence is lower compared to CTLA-4 inhibitors. Adverse events such as fatigue, rash, diarrhea, pneumonitis, and endocrine dysfunction should be carefully monitored and managed to ensure patient safety during PD-1/PD-L1 inhibitor treatment.

In summary, the findings of this review are consistent with previous studies and support the potential of PD-1/PD-L1 inhibitors, particularly pembrolizumab, in improving treatment outcomes for patients with breast cancer, especially in the advanced TNBC subtype. The ongoing research and exploration of PD-1/PD-L1 inhibitors in early-stage breast cancer and other subtypes hold promise for further enhancing patient outcomes. However, challenges in patient selection, managing adverse events, and addressing resistance mechanisms need to be addressed to optimize the use of PD-1/PD-L1 inhibitors in breast cancer treatment.

Conclusions

The PD-1/PD-L1 pathway is pivotal in maintaining immune homeostasis and is exploited by tumor cells in the TME to evade immune responses. PD-1/PD-L1 inhibitors have the potential to restore anti-tumor immune responses by blocking the interaction between PD-1 and PD-L1, allowing the immune system to recognize and attack tumor cells. These inhibitors have demonstrated efficacy in various cancers, showing promise in different tumor types, treatment routes, drug combinations, and regimens.

However, the application of PD-1/PD-L1 inhibitors in breast cancer presents challenges. The response to these inhibitors can vary, and not all patients benefit, with some exhibiting primary or acquired resistance. The correlation between PD-L1 expression in tumor cells and response to inhibitors is not consistent, indicating that PD-L1 expression alone may not be a reliable biomarker for predicting therapeutic efficacy. The identification of reliable predictive biomarkers for patient selection and treatment response monitoring remains a critical area of ongoing research and development in the field of breast cancer treatment.

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