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Case-Based Analysis of Breast Cancer Immunotherapy: Efficacy, Challenges, and Future Directions

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Abstract This study evaluates the efficacy, challenges, and future directions of breast cancer immunotherapy, with a particular focus on immune checkpoint inhibitors (ICIs), CAR-T cell therapy, cancer vaccines, and monoclonal antibodies. Key findings indicate that while ICIs, especially in combination with chemotherapy, has demonstrated durable responses, its efficacy as a monotherapy remains limited, particularly in triple-negative breast cancer (TNBC). Case-based analyses reveal the potential of personalized immunotherapy approaches, such as adoptive cell transfer and neoadjuvant immunotherapy, in achieving significant clinical outcomes even in treatment-resistant cases. However, significant challenges persist, including tumor heterogeneity, immune evasion mechanisms, adverse effects, and the need for robust predictive biomarkers. The study highlights the potential of combination strategies and innovative therapies, such as bi-specific antibodies and oncolytic virus therapy, to overcome these barriers. Future research must focus on identifying precise biomarkers, understanding resistance mechanisms, and developing novel immunotherapeutic approaches to improve patient outcomes. This comprehensive analysis underscores the promising potential of immunotherapy in breast cancer treatment and the need for ongoing innovation and research to address existing challenges.

Keywords Breast cancer; Immunotherapy; Immune checkpoint inhibitors (ICIs); Triple-negative breast cancer (TNBC); Predictive biomarkers

1 Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide and remains a leading cause of cancer-related deaths (Basu et al., 2019; García-Aranda and Redondo, 2019; Hu et al., 2023). In 2020 alone, there were an estimated 2.3 million new cases and 685 000 deaths attributed to breast cancer globally (Luo et al., 2022). Historically, the treatment of breast cancer has relied heavily on surgery, radiation, and systemic therapies such as chemotherapy and hormone therapy. These conventional treatments have significantly improved patient outcomes, yet challenges such as tumor heterogeneity, treatment resistance, and disease recurrence persist (Basu et al., 2019; Venetis et al., 2020).

The advent of immunotherapy has revolutionized cancer treatment by harnessing the body's immune system to target and destroy cancer cells. Immunotherapy has shown remarkable success in treating various cancers, including melanoma and non-small cell lung cancer (NSCLC) (Mina et al., 2019). In breast cancer, the approval of immune checkpoint inhibitors (ICIs) such as atezolizumab and pembrolizumab has marked a significant milestone, particularly for patients with triple-negative breast cancer (TNBC) (García-Aranda and Redondo, 2019; Henriques et al., 2021; Luo et al., 2022). These therapies work by blocking inhibitory pathways that prevent immune cells from attacking cancer cells, thereby enhancing the anti-tumor immune response.

The introduction of immunotherapy has significantly impacted the breast cancer treatment landscape. For instance, the combination of ICIs with chemotherapy has shown promising results in improving survival rates for patients with metastatic TNBC (García-Aranda and Redondo, 2019; Luo et al., 2022; Hu et al., 2023). Additionally, other immunotherapeutic approaches such as monoclonal antibodies, adoptive cell therapy, and therapeutic vaccines are being actively explored and have shown potential in preclinical and clinical studies (Basu et al., 2019; Venetis et al., 2020; Agostinetto et al., 2022). Despite these advancements, the efficacy of immunotherapy in breast cancer is

still limited by factors such as poor immunogenicity and the immunosuppressive tumor microenvironment (Monnot and Romero, 2018; Basu et al., 2019).

This study is to provide a comprehensive analysis of the current state of breast cancer immunotherapy, focusing on its efficacy, challenges, and future directions. By examining case-based studies and clinical trials, we seek to elucidate the factors that influence the success of immunotherapy in breast cancer and identify potential strategies to overcome existing barriers. The scope of this study includes an evaluation of various immunotherapeutic modalities, their clinical outcomes, and the ongoing research efforts aimed at enhancing the therapeutic efficacy of immunotherapy in breast cancer.

2 Overview of Breast Cancer Immunotherapy

2.1 Types of immunotherapy

2.1.1 Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) are a class of drugs that block proteins used by cancer cells to evade the immune system. The most notable ICIs target CTLA-4, PD-1, and PD-L1 pathways. These inhibitors have shown remarkable success in treating various cancers, including breast cancer, by enhancing the immune response against tumor cells (Esteva et al., 2019; Macri and Mintern, 2019). Bagchi et al. (2020) has shown that the high frequencies of memory CD4+ and CD8+ T cells before and after ICI treatment is associated with a good response to treatment. However, the mechanism by which these T cells promote favorable therapeutic outcomes is still unclear. In addition, different TCR libraries are also associated with effective treatment (Figure 1). However, the efficacy of ICIs in breast cancer has been limited, necessitating combination strategies to improve outcomes (Darvin et al., 2018).

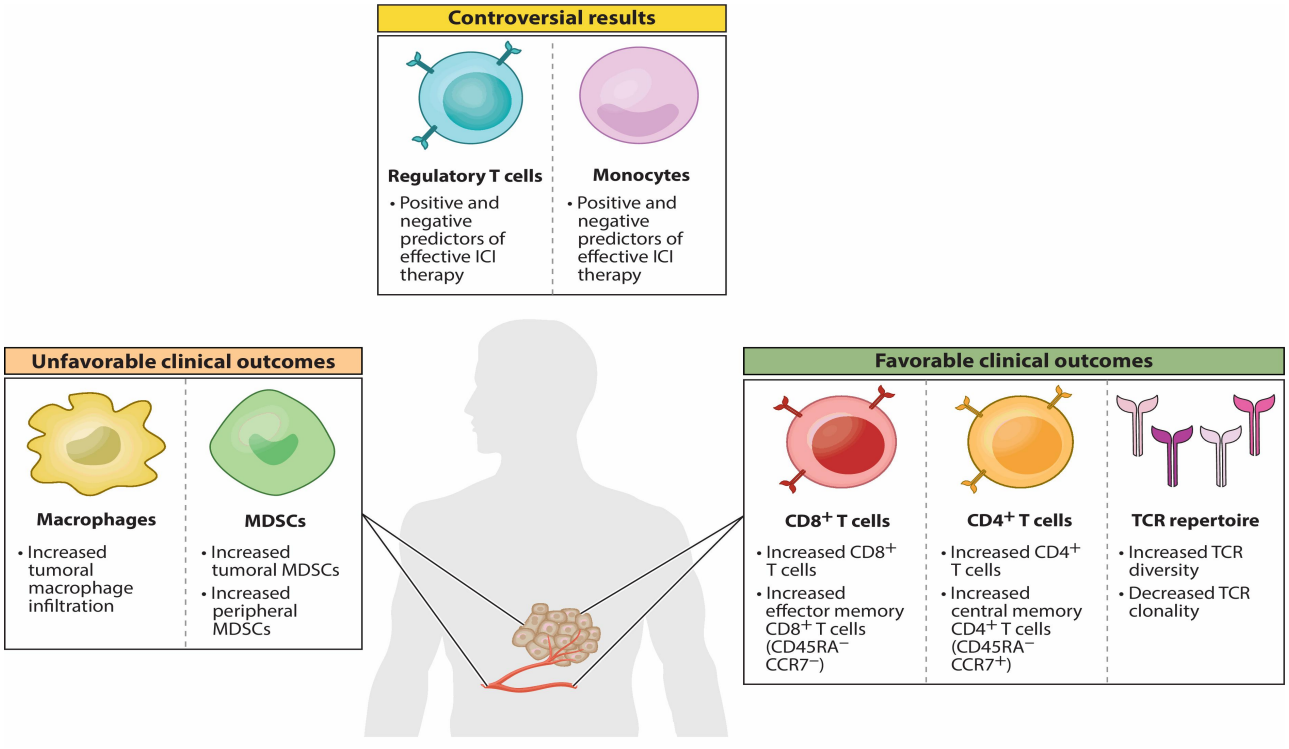

Figure 1 The immune cell types and their correlation to ICI therapy outcome (Adopted from Bagchi et al., 2020)

Image caption: ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell; NSCLC, non-small-cell lung cancer; TCR, T cell receptor; Treg, regulatory T cell (Adopted from Bagchi et al., 2020).

2.1.2 CAR-T cell therapy

Chimeric Antigen Receptor (CAR) T-cell therapy involves genetically modifying a patient's T cells to express receptors specific to cancer antigens. This approach has shown dramatic results in hematological malignancies and is being explored for solid tumors, including breast cancer (Khalil et al., 2016; Lohmueller and Finn, 2017).

Despite its potential, CAR-T cell therapy faces challenges such as limited efficacy in solid tumors and severe side effects (Macri and Mintern, 2019).

2.1.3 Cancer vaccines

Cancer vaccines aim to stimulate the immune system to recognize and attack cancer cells. These vaccines can be prophylactic or therapeutic. While therapeutic cancer vaccines have had limited success historically, recent advancements suggest potential when used in combination with other immunotherapies (Lohmueller and Finn, 2017). Prophylactic vaccines are also being developed to prevent cancer in high-risk populations (Lohmueller and Finn, 2017).

2.1.4 Monoclonal antibodies

Monoclonal antibodies (mAbs) are laboratory-produced molecules that can bind to specific antigens on cancer cells. They can work through various mechanisms, including blocking growth signals, marking cancer cells for destruction by the immune system, and delivering cytotoxic agents directly to cancer cells. mAbs have been particularly effective in HER2-positive breast cancer, with drugs like trastuzumab significantly improving patient outcomes (Khalil et al., 2016; Agostinetto et al., 2022).

2.2 Mechanisms of action

The mechanisms of action for breast cancer immunotherapies vary depending on the type of therapy. ICIs work by blocking inhibitory pathways that prevent T cells from attacking cancer cells, thereby enhancing the immune response (Esteva et al., 2019; Bagchi et al., 2020). CAR-T cell therapy involves the direct targeting and killing of cancer cells by engineered T cells (Khalil et al., 2016). Cancer vaccines stimulate the immune system to recognize and attack cancer cells, either by presenting cancer antigens or by enhancing the overall immune response (Lohmueller and Finn, 2017). Monoclonal antibodies can block growth signals, recruit immune cells to destroy cancer cells, or deliver cytotoxic agents directly to the tumor (Khalil et al., 2016; Adams et al., 2019).

2.3 Historical context and development

The concept of using the immune system to fight cancer dates back over a century, but significant breakthroughs have only occurred in the past decade. The approval of the first immune checkpoint inhibitor, anti-CTLA-4, in 2011 marked a turning point in cancer immunotherapy (Macri and Mintern, 2019; Bagchi et al., 2020). Since then, numerous ICIs, CAR-T cell therapies, and monoclonal antibodies have been developed and approved for various cancers, including breast cancer (Khalil et al., 2016; Esteva et al., 2019). The development of these therapies has been driven by a deeper understanding of the immune system and its interactions with cancer cells, as well as advances in genetic engineering and biotechnology (Lohmueller and Finn, 2017; Macri and Mintern, 2019).

3 Case-Based Efficacy Analysis

3.1 Case 1: complete durable regression in metastatic breast cancers

In a groundbreaking study by Zacharakis et al. (2018), the efficacy of adoptive cell transfer (ACT) utilizing tumor-infiltrating lymphocytes (TILs) was demonstrated in a patient with metastatic breast cancer. The patient, who had previously undergone extensive conventional treatments without significant success, exhibited a complete durable regression following ACT. The treatment involved the extraction, expansion, and reinfusion of TILs specifically targeting mutant proteins expressed by the tumor. Remarkably, the patient achieved a sustained remission, with no detectable cancer cells for an extended period post-treatment. This case underscores the potential of personalized immunotherapy approaches in achieving significant clinical outcomes in advanced metastatic breast cancers.

3.2 Case 2: neoadjuvant immunotherapy in triple-negative breast cancer

Zhao et al. (2023) investigated the application of neoadjuvant immunotherapy in patients with triple-negative breast cancer (TNBC), a subtype notoriously resistant to conventional treatments. The study involved a combination of pembrolizumab, an immune checkpoint inhibitor, administered prior to surgical resection. The results were promising, with a significant proportion of patients achieving a pathological complete response (pCR), indicating no residual invasive cancer detectable in the breast or lymph nodes (Figure 2). This response is

particularly noteworthy given the aggressive nature of TNBC and its typical resistance to other forms of chemotherapy. The findings from this case highlight the potential for neoadjuvant immunotherapy to transform the treatment landscape for TNBC, improving both survival rates and quality of life for patients.

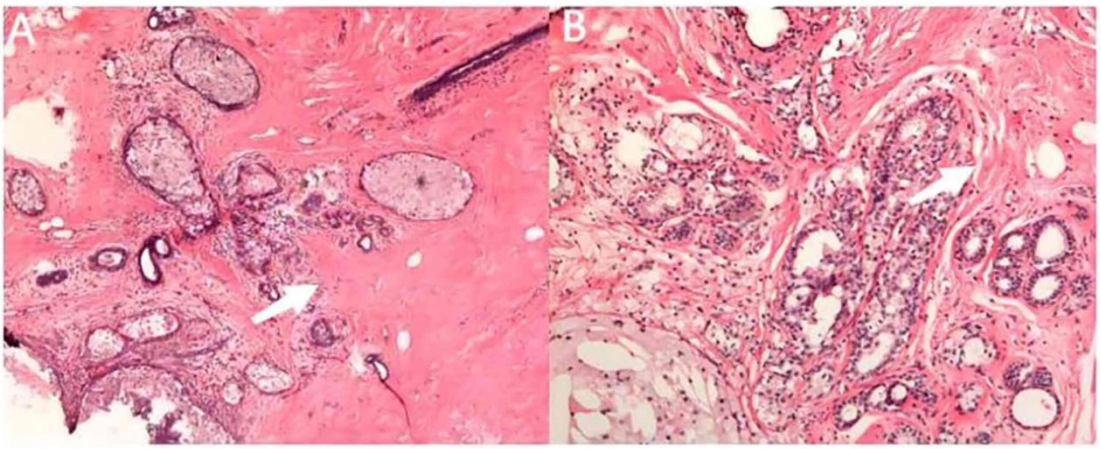

Figure 2 Pathological complete response of the breast and stromal hyaline degeneration after six cycles of neoadjuvant therapy (Adopted from Zhao et al., 2023)

Image caption: H&E staining at (A) ×40 magnification and (B) ×100 magnification. Arrows indicate stromal hyaline degeneration (Adopted from Zhao et al., 2023)

3.3 Case 3: regression of lymph node metastases with dendritic cell therapy

In a seminal study by Kobayashi et al. (2001), the efficacy of dendritic cell (DC) therapy was evaluated in a patient with lymph node metastases from breast cancer. The patient received DCs pulsed with tumor-associated antigens, designed to activate the immune system against cancer cells. The treatment led to a significant regression of metastatic lesions in the lymph nodes, demonstrating the capacity of DC therapy to induce robust anti-tumor immune responses. This case provided early evidence supporting the feasibility and potential effectiveness of DC-based immunotherapies in treating metastatic breast cancer, paving the way for subsequent research and clinical trials in this area.

These cases collectively illustrate the diverse and promising applications of immunotherapy in treating different subtypes and stages of breast cancer. They underscore the potential for these innovative treatments to achieve significant clinical benefits, even in cases where conventional therapies have failed. As research progresses, these approaches are expected to become increasingly refined and effective, offering hope for improved outcomes in breast cancer patients.

4 Challenges in Breast Cancer Immunotherapy

4.1 Tumor heterogeneity

Tumor heterogeneity in breast cancer presents a significant challenge to the efficacy of immunotherapy. The genetic, histopathological, and molecular diversity within and between tumors can lead to varied responses to treatment. This heterogeneity is particularly pronounced in triple-negative breast cancer (TNBC), which exhibits high genomic instability and mutation rates, contributing to the creation of neoantigens and enhanced immunogenicity (Kúdelová et al., 2022). The complex and heterogeneous tumor immune microenvironment, characterized by disorganized gene expression and altered signaling pathways, further complicates treatment (Kúdelová et al., 2022). Additionally, the variability in immune cell infiltration and the presence of different tumor subtypes within a single patient can result in inconsistent responses to immunotherapy (Bai et al., 2020).

4.2 Immune evasion mechanisms

Breast cancer tumors employ multiple mechanisms to evade immune surveillance, which significantly hampers the success of immunotherapy. These mechanisms include immunosuppression via cytokines like interleukin 10 (IL-10) and tumor growth factor beta (TGF-β), induction of tolerance through immune checkpoints such as CTLA-4 and PD-1/PD-L1, and resistance to apoptosis by expressing anti-apoptotic molecules (Bou-Dargham et

al., 2018). Tumors can also impair antigen presentation and create an immunosuppressive tumor microenvironment, which further aids in immune evasion (Bou-Dargham et al., 2018; Elsas et al., 2020). The complexity of these mechanisms necessitates a deeper understanding to develop more effective immunotherapeutic strategies.

4.3 Adverse effects and toxicity

The adverse effects and toxicity associated with immunotherapy are significant barriers to its widespread use in breast cancer treatment. Immune checkpoint inhibitors, for instance, can lead to immune-related adverse events (irAEs) that affect various organs and systems, causing conditions such as colitis, dermatitis, and endocrinopathies (Henriques et al., 2021). The severity of these side effects can limit the dosage and duration of treatment, thereby reducing its efficacy. Moreover, the management of these toxicities requires careful monitoring and may necessitate the use of immunosuppressive drugs, which can counteract the benefits of immunotherapy (Basu et al., 2019; Henriques et al., 2021).

4.4 Patient selection and biomarkers

Identifying the right patients who are most likely to benefit from immunotherapy remains a critical challenge. Current biomarkers, such as PD-L1 expression, are not always reliable predictors of response, as not all PD-L1 positive patients respond to treatment, and some PD-L1 negative patients do (Bou-Dargham et al., 2018). Ende et al. (2023) have been investigated for their correlation with pCR rate (Figure 3). Despite the large number of studies investigating which biomarkers are associated with a pCR, no ideal marker has reached the robustness and confidence to become widely implemented in clinical practice. The heterogeneity in immune evasion mechanisms among breast cancer patients further complicates the selection process. There is a pressing need for more precise biomarkers that can accurately predict response to immunotherapy and guide treatment decisions (Bou-Dargham et al., 2018; Retecki et al., 2021).

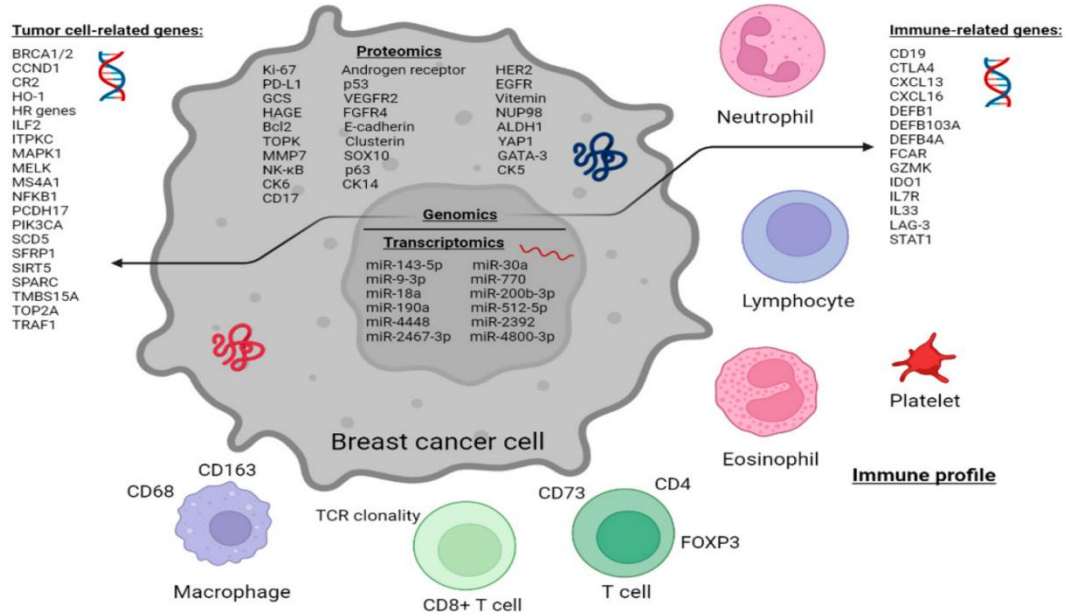

Figure 3 Schematic representation of putative predictive markers linked to pCR after NAC in TNBC patients (Adopted from Ende et al., 2023)

4.5 Resistance to immunotherapy

Resistance to immunotherapy, both primary and acquired, is a major hurdle in the treatment of breast cancer. Primary resistance occurs when patients do not respond to immunotherapy from the outset, while acquired resistance develops after an initial period of response (Bai et al., 2020; Hanna and Balko, 2021). The mechanisms underlying resistance are multifaceted, involving tumor-intrinsic factors such as genetic mutations and tumor-extrinsic factors like the immunosuppressive tumor microenvironment (Bai et al., 2020). Understanding

these mechanisms is crucial for developing strategies to overcome resistance and improve patient outcomes (Elsas et al., 2020; Hanna and Balko, 2021).

4.6 Economic and accessibility issues

The high cost of immunotherapy poses significant economic and accessibility challenges. The development and administration of these treatments are expensive, making them inaccessible to many patients, particularly in low- and middle-income countries (Hegde and Chen, 2020). Additionally, the need for specialized infrastructure and trained personnel to administer and monitor immunotherapy further limits its availability. Addressing these economic and accessibility issues is essential to ensure that the benefits of immunotherapy can be extended to a broader patient population (Hegde and Chen, 2020).

5 Future Development Trends in Breast Cancer Immunotherapy

5.1 Emerging therapies and combination treatments

5.1.1 Combination with chemotherapy

Combining immunotherapy with traditional chemotherapy has shown promise in enhancing the efficacy of cancer treatments. Chemotherapy can modulate the tumor microenvironment, making it more susceptible to immune attack. For instance, the use of immune checkpoint inhibitors in conjunction with chemotherapy has demonstrated improved outcomes in various cancers, including breast cancer (Khalil et al., 2016; Bou-Dargham et al., 2021). This combination approach aims to leverage the cytotoxic effects of chemotherapy to reduce tumor burden while simultaneously activating the immune system to target residual cancer cells.

5.1.2 Combination with targeted therapies

Targeted therapies, such as those inhibiting specific molecular pathways, can be effectively combined with immunotherapy to enhance treatment efficacy. For example, combining PARP inhibitors with immune checkpoint inhibitors has shown potential in treating triple-negative breast cancer (TNBC) (Bou-Dargham et al., 2021). This combination exploits the DNA damage response pathway to increase tumor immunogenicity, thereby enhancing the immune response against cancer cells. Additionally, combining CAR-T cell therapy with small molecule drugs has been explored to overcome the limitations of CAR-T cells in solid tumors (Nguyen et al., 2022).

5.2 Personalized and precision immunotherapy

Personalized immunotherapy, tailored to the genetic and molecular profile of individual patients, represents a significant advancement in breast cancer treatment. By utilizing next-generation sequencing and other molecular diagnostic tools, clinicians can identify specific tumor antigens and immune evasion mechanisms unique to each patient. This approach allows for the development of highly specific immunotherapies, such as neoantigen vaccines and personalized CAR-T cells, which can provide more effective and durable responses (Pan et al., 2020).

5.3 Innovations in biomarkers and diagnostic tools

The identification and validation of biomarkers are crucial for predicting patient response to immunotherapy and monitoring treatment efficacy. Recent advancements in biomarker discovery have focused on identifying immune-related markers, such as PD-L1 expression and tumor mutational burden, which can guide the selection of appropriate immunotherapeutic agents (Whiteside et al., 2016; Sivaganesh et al., 2021). Additionally, non-invasive diagnostic tools, such as liquid biopsies, are being developed to monitor treatment response and detect early signs of resistance, enabling timely adjustments to therapeutic strategies (Whiteside et al., 2016).

5.4 Advances in CAR-T cell therapy

CAR-T cell therapy has revolutionized the treatment of hematological malignancies and is now being explored for solid tumors, including breast cancer. Recent innovations in CAR-T cell engineering, such as the development of "armored" CAR-T cells and dual-targeting CARs, aim to enhance their efficacy and overcome the immunosuppressive tumor microenvironment (Khalil et al., 2016; Nguyen et al., 2022; Schepisi et al., 2023). These advancements include the incorporation of cytokine support and immune checkpoint blockade within CAR-T cells to improve their persistence and anti-tumor activity (Wang and Zhou, 2017; Schepisi et al., 2023).

5.5 Role of artificial intelligence in treatment planning

Artificial intelligence (AI) is playing an increasingly important role in the planning and optimization of cancer immunotherapy. AI algorithms can analyze vast amounts of clinical and molecular data to identify patterns and predict patient responses to different immunotherapeutic agents. This capability enables the development of personalized treatment plans that maximize efficacy and minimize adverse effects (Pan et al., 2020). Additionally, AI can assist in the discovery of new immunotherapy targets and the design of novel therapeutic strategies, accelerating the pace of innovation in breast cancer treatment (Pan et al., 2020).

6 Potential Innovative Directions in Breast Cancer Immunotherapy

6.1 Novel immunotherapeutic approaches

6.1.1 Bi-specific antibodies

Bi-specific antibodies are engineered to simultaneously bind to two different antigens, enhancing the specificity and efficacy of targeting cancer cells. In breast cancer, bi-specific antibodies can be designed to target tumor-associated antigens and engage immune effector cells, such as T cells, to promote a more robust anti-tumor response. This approach has shown promise in preclinical studies and early-phase clinical trials, offering a potential new avenue for breast cancer treatment (Shi et al., 2020; Barzaman et al., 2021).

6.1.2 Oncolytic virus therapy

Oncolytic viruses (OVs) selectively infect and lyse cancer cells while sparing normal tissues. These viruses not only directly kill tumor cells but also stimulate systemic anti-tumor immune responses. Combining OVs with other immunotherapies, such as immune checkpoint inhibitors or CAR-T cells, has shown enhanced efficacy in preclinical models and clinical trials. This combinatorial approach aims to overcome the immunosuppressive tumor microenvironment and improve therapeutic outcomes in breast cancer (Raja et al., 2018; Shi et al., 2020).

6.1.3 Adoptive T cell transfer

Adoptive T cell transfer involves the isolation and ex vivo expansion of tumor-infiltrating lymphocytes (TILs) or genetically engineered T cells, such as CAR-T cells, which are then reinfused into the patient. This strategy has demonstrated significant clinical benefits in various cancers, including breast cancer. The ability to engineer T cells to target specific tumor antigens holds great promise for personalized cancer therapy (Alard et al., 2020; Zhang and Zhang, 2020; Barzaman et al., 2021).

6.2 Integration of multi-omics data for personalized therapy

The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, can provide a comprehensive understanding of the molecular landscape of breast cancer. This approach enables the identification of novel biomarkers and therapeutic targets, facilitating the development of personalized immunotherapy regimens. By tailoring treatments to the unique molecular profile of each patient's tumor, it is possible to enhance the efficacy and reduce the adverse effects of immunotherapy (Zhang and Zhang, 2020; Barzaman et al., 2021).

6.3 Enhancing immune system engagement

6.3.1 Modulating the tumor microenvironment

The tumor microenvironment (TME) plays a critical role in immune evasion and tumor progression. Strategies to modulate the TME, such as targeting immune-suppressive cells (e.g., regulatory T cells, myeloid-derived suppressor cells) or altering the metabolic landscape, can enhance the anti-tumor immune response. Recent advances in understanding the TME have led to the development of novel agents that can reprogram the TME to support immune activation and improve the efficacy of immunotherapies (Esteva et al., 2019; Guerra et al., 2020; Rameshbabu et al., 2021).

6.3.2 Combination strategies with other novel therapies

Combining immunotherapy with other treatment modalities, such as targeted therapy, chemotherapy, or radiotherapy, can synergistically enhance anti-tumor responses. For instance, combining immune checkpoint inhibitors with HER2-targeted therapies or PARP inhibitors has shown promising results in breast cancer. These combination strategies aim to overcome resistance mechanisms and achieve more durable clinical responses (Adams et al., 2019; Esteva et al., 2019; Shi et al., 2020).

6.4 Use of nanotechnology in immunotherapy delivery

Nanotechnology offers innovative solutions for the delivery of immunotherapeutic agents. Nanoparticles can be engineered to improve the stability, bioavailability, and targeted delivery of immunotherapies, reducing off-target effects and enhancing therapeutic efficacy. In breast cancer, nanotechnology-based delivery systems are being explored to optimize the administration of immune checkpoint inhibitors, vaccines, and other immunotherapeutic agents, potentially transforming the landscape of cancer treatment (Gajewski, 2015; Barzaman et al., 2021).

7 Concluding Remarks

This study has highlighted the significant progress and ongoing challenges in the field of breast cancer immunotherapy. Key findings include the efficacy of immune checkpoint inhibitors (ICIs) in producing durable responses, particularly when used in combination with chemotherapy. The study also underscores the limited effectiveness of ICIs as monotherapy, especially in triple-negative breast cancer (TNBC). Promising results have been observed with combination strategies that integrate dendritic cell vaccines and targeted therapies, demonstrating enhanced anti-tumor immune responses. However, persistent challenges such as poor immunogenicity, inadequate T-cell infiltration, and heightened immunosuppression within the tumor microenvironment continue to impede the success of immunotherapy. Additionally, the identification of robust predictive biomarkers for immunotherapy response remains an ongoing challenge.

The findings from this study have several implications for clinical practice. First, the combination of ICB with chemotherapy or other therapeutic modalities should be considered to improve patient outcomes, particularly in early-stage and metastatic breast cancer. The approval of atezolizumab combined with nab-paclitaxel for PD-L1-positive metastatic TNBC highlights the potential of immunotherapy in specific patient subsets. Clinicians should also be aware of the predictive factors such as PD-L1 expression, tumor-infiltrating lymphocytes (TILs), and CD8+ T-cell levels, which can guide treatment decisions and improve response rates. Furthermore, the integration of immunotherapy in the neoadjuvant setting for high-risk TNBC patients has shown significant improvements in pathological complete response (pCR) rates, suggesting a potential shift in treatment paradigms.

Future research should focus on several key areas to advance the field of breast cancer immunotherapy. First, there is a need for the development and validation of robust predictive biomarkers to identify patients who are most likely to benefit from immunotherapy. Additionally, further studies are required to explore the mechanisms of resistance to immunotherapy and to develop strategies to overcome these barriers. The potential of novel immunotherapeutic approaches, such as cancer vaccines and adoptive T-cell therapies, should be investigated in larger, randomized clinical trials to establish their efficacy and safety. Finally, the combination of immunotherapy with emerging technologies such as nanotechnology and radiotherapy warrants further exploration to enhance treatment efficacy and broaden the therapeutic options for breast cancer patients.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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