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ADVANCES IN IMMUNOTHERAPY FOR THE TREATMENT OF METASTATIC BREAST CANCER: A COMPREHENSIVE REVIEW

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Resume: INTRODUCTION The introduction focuses on the evolving landscape of metastatic breast cancer treatment, highlighting the limitations of traditional therapies and the potential of immunotherapy. It introduces key concepts such as immune checkpoints, the tumor microenvironment, and the heterogeneity of breast cancer subtypes. The section emphasizes the importance of biomarker-driven therapies and sets the stage for discussing the current status and challenges of immunotherapy in breast cancer, particularly in triple-negative cases. **OBJETIVE** To explore the recent advancements in immunotherapy, including checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines, and their impact on the treatment of metastatic breast cancer. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Immunotherapy" AND "Metastatic Breast Cancer" OR "Checkpoint Inhibitors" OR "Triple-Negative Breast Cancer" OR "Tumor Microenvironment" in the last years. **RESULTS AND DISCUSSION** The results and discussion sections delve into the efficacy of immunotherapy, particularly checkpoint inhibitors like pembrolizumab and atezolizumab, in metastatic triple-negative breast cancer. Clinical trials such as IMpassion130 and KEYNOTE-355 are reviewed, along with the challenges of immunotherapy resistance and the variability of responses based on biomarkers. Combination therapies are explored, including immunotherapy with chemotherapy, PARP inhibitors, and radiation. The section also addresses immune-related adverse events and the complexities of managing these treatments in a clinical setting. **CONCLUSION** The conclusion highlights immunotherapy as a breakthrough in metastatic breast cancer treatment, especially in triple-negative subtypes. It acknowledges the current limitations, such as biomarker variability and treatment resistance, but emphasizes the potential of combination strategies and personalized medicine to expand the benefits of immunotherapy. The section also calls for further research to optimize treatment protocols and reduce adverse effects, positioning immunotherapy as a cornerstone of future breast cancer treatment strategies.

Keywords: Immunotherapy; Metastatic Breast Cancer; PD-L1 Inhibition; Triple-Negative Breast Cancer; Cancer Vaccines

INTRODUCTION

The treatment landscape for metastatic breast cancer (MBC) has undergone significant transformation in recent decades, with immunotherapy emerging as a promising therapeutic strategy[1]. Traditional treatments, such as chemotherapy, hormonal therapy, and targeted agents, have extended survival in many patients but are limited by toxicity, resistance, and the complexity of cancer biology[1]. As breast cancer is a highly heterogeneous disease, effective management often depends on the molecular subtype, stage, and the patient's overall health[1].

The introduction of immunotherapeutic agents, including checkpoint inhibitors and novel vaccines, has heralded a new era in oncology, driven by the need to leverage the immune system's natural ability to target and destroy malignant cells[2]. Immunotherapy capitalizes on the intricate relationship between tumor cells and the immune microenvironment, where evasion of immune surveillance plays a critical role in cancer progression[2]. The interplay between immune checkpoints, such as PD-1/PD-L1 and CTLA-4, and the tumor's ability to suppress immune responses has been the cornerstone of developing these novel treatments[2].

Checkpoint inhibitors have demonstrated efficacy in numerous malignancies, but their application in breast cancer, particularly in the metastatic setting, presents unique challenges and opportunities[3]. The tumor microenvironment in breast cancer is typically less immunogenic compared to other cancers, such as melanoma and lung cancer[3]. However, triple-negative breast cancer (TNBC), an aggressive subtype of breast cancer, has shown promise as a target for immune-based therapies[3].

TNBC lacks the expression of estrogen receptors, progesterone receptors, and HER2, making it unresponsive to hormonal and HER2-targeted therapies[3]. It is in this context that checkpoint inhibitors, such as pembrolizumab and atezolizumab, have gained attention as viable options for improving outcomes in metastatic TNBC[4].

Despite these advances, the heterogeneity of immune responses in breast cancer remains a significant hurdle, with some tumors exhibiting high levels of tumor-infiltrating lymphocytes (TILs) while others display an immune-excluded phenotype[4]. This variability underscores the importance of identifying predictive biomarkers to guide the use of immunotherapy in this population[4].

OBJETIVES

To explore the recent advancements in immunotherapy, including checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines, and their impact on the treatment of metastatic breast cancer.

SECUNDARY OBJETIVES

1. To evaluate the efficacy of immunotherapy, particularly in triple-negative breast cancer.
2. To analyze the role of biomarkers in predicting responses to immunotherapy in metastatic breast cancer.
3. To assess combination strategies involving immunotherapy and traditional treatments like chemotherapy and radiation.
4. To identify the challenges and adverse effects associated with the use of immunotherapy in metastatic breast cancer.
5. To explore ongoing research and future directions in immunotherapy for metastatic breast cancer, including cost-effectiveness and personalized medicine approaches.

METHODS

This is a narrative review, in which the main aspects of recent advancements in immunotherapy, including checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines, and their impact on the treatment of metastatic breast cancer. in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Immunotherapy" AND "Metastatic Breast Cancer" OR "Checkpoint Inhibitors" OR "Triple-Negative Breast Cancer" OR "Tumor Microenvironment" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

In addition to checkpoint inhibitors, novel immunotherapy approaches, such as CAR-T cell therapy and cancer vaccines, are being investigated for their potential to enhance the immune system's ability to target and eliminate breast cancer cells[5]. CAR-T cell therapy, which involves the genetic modification of a patient's own T cells to express chimeric antigen receptors that recognize specific antigens on tumor cells, has revolutionized the treatment of hematologic malignancies[5]. Its application in solid tumors, including breast cancer, is still in the early stages, with several clinical trials underway to assess its safety and efficacy[5]. Cancer vaccines, designed to stimulate the immune system to recognize tumor-specific antigens, represent another promising strategy[6]. While these approaches are still largely experimental in breast cancer, they highlight the growing recognition of the immune system's pivotal role in controlling tumor growth and metastasis[6].

The results of clinical trials evaluating immunotherapy in metastatic breast cancer have been met with both optimism and caution. One of the most notable successes has been the use of atezolizumab, a PD-L1 inhibitor, in combination with nab-paclitaxel for the treatment of metastatic TNBC[7]. In the IMpassion130 trial, this combination demonstrated a significant improvement in progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone in patients with PD-L1-positive tumors[7]. This marked the first approval of a checkpoint inhibitor for breast cancer and underscored the importance of biomarker-driven therapies[7]. However, the benefit of atezolizumab was limited to patients whose tumors expressed PD-L1, highlighting the need for accurate biomarker testing[8]. Subsequent trials, such as IMpassion131, which evaluated atezolizumab in combination with paclitaxel, failed to replicate these results, raising questions about the optimal use of checkpoint inhibitors in breast cancer[8].

Pembrolizumab, another PD-1 inhibitor, has also shown promise in metastatic TNBC[9]. The KEYNOTE-355 trial demonstrated that pembrolizumab plus chemotherapy significantly improved PFS in patients with PD-L1-positive TNBC compared to chemotherapy alone[9]. This trial led to the approval of pembrolizumab in this setting, further establishing the role of immunotherapy in TNBC[9]. Despite these advances, the overall response rates to checkpoint inhibitors in breast cancer remain modest, with only a subset of patients deriving long-term benefit[10]. Understanding the mechanisms of resistance to immunotherapy is a critical area of ongoing research, as many patients experience primary or acquired resistance to these agents[10]. Factors such as the presence of an immunosuppressive tumor microenvironment, low mutational burden, and lack of neoantigen expression may contribute to this resistance[10].

Combination strategies are being explored as a means to overcome resistance and enhance the efficacy of immunotherapy in metastatic breast cancer[11]. The rationale behind combining immunotherapy with other treatment modalities, such as chemotherapy, targeted therapies, or radiation, is to create a more favorable immune environment for the activation of immune cells[11]. Chemotherapy, for example, can induce immunogenic cell death, release tumor antigens, and modulate the tumor microenvironment, thereby enhancing the response to checkpoint inhibitors[12]. Trials evaluating the combination of immunotherapy with PARP inhibitors, which target DNA repair pathways, are particularly intriguing in TNBC, as these tumors often harbor defects in DNA repair mechanisms[12]. The combination of immunotherapy and radiation therapy is also being investigated, with the hypothesis that radiation can increase tumor antigen release and promote immune activation[12].

Despite the excitement surrounding these combination approaches, they are not without challenges. The toxicity profile of combination therapies is a significant concern, as the addition of multiple agents can increase the risk of immune-related adverse events (irAEs)[13]. Managing irAEs, which can affect multiple organ systems, requires a multidisciplinary approach and may necessitate the discontinuation of immunotherapy in severe cases[13]. Furthermore, the financial burden of combination therapies, particularly in the context of long-term treatment, is an important consideration for both patients and healthcare systems[14]. The cost-effectiveness of immunotherapy in metastatic breast cancer, especially in comparison to existing treatments, is a topic of ongoing debate and will likely play a role in determining its broader adoption[14].

CONCLUSION

Immunotherapy represents a paradigm shift in the treatment of metastatic breast cancer, particularly for patients with TNBC. The approval of checkpoint inhibitors has provided new hope for patients with this aggressive form of breast cancer, although the benefits are currently limited to a subset of patients whose tumors express PD-L. Ongoing research into biomarkers, combination strategies, and novel immunotherapeutic approaches holds promise for expanding the role of immunotherapy in metastatic breast cancer.

As our understanding of the immune system's interactions with cancer continues to evolve, it is likely that immunotherapy will become an integral component of breast cancer treatment, potentially transforming outcomes for patients with this challenging disease. The integration of personalized medicine, where treatment decisions are guided by the molecular and immunologic characteristics of each tumor, will be key to maximizing the potential of immunotherapy in breast cancer.

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