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The Application of Immunotherapy in Thyroid Cancer Research

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Abstract: ***Thyroid cancer is the most common endocrine malignancy globally, with differentiated thyroid cancer (DTC) accounting for 90% of cases. However, advanced and anaplastic thyroid cancer (ATC) still lack effective treatment options. In recent years, immunotherapy has demonstrated potential in refractory thyroid cancer by activating anti-tumor immune responses. This article reviews the clinical progress of strategies such as immune checkpoint inhibitors (ICIs), adoptive cell therapy (ACT), and tumor vaccines, and discusses their biomarkers and mechanisms of drug resistance.***

Keywords: Thyroid cancer; Immunotherapy; Biomarkers; Mechanisms of drug resistance.

1. INTRODUCTION

Thyroid cancer, recognized as the most prevalent endocrine-related cancer globally, significantly endangers individuals' well-being. Among its various forms, differentiated thyroid cancer (DTC) represents approximately 90% of all instances, establishing it as the primary category. While DTC often carries a favorable prognosis, managing advanced stages and anaplastic thyroid cancer (ATC) remains a formidable challenge, with limited effective treatments available, adversely affecting survival rates. In the quest for novel therapeutic approaches, immunotherapy has recently surfaced as a groundbreaking method that stimulates the body's immune response against tumors, showing promising prospects in addressing treatment-resistant thyroid cancer. This method works by adjusting and boosting the patient's immune system to better identify and combat cancer cells, offering fresh therapeutic possibilities for those affected. Notably, among the array of immunotherapy tactics, inhibitors targeting immune checkpoints (ICIs), cell-based therapies like adoptive cell therapy (ACT), and vaccines designed to target tumors have received significant focus. These approaches have achieved notable advancements in clinical settings, enhancing treatment efficacy for thyroid cancer patients and providing new perspectives on the immunological aspects of the disease. Additionally, the exploration of biomarkers and the investigation into resistance mechanisms are crucial for refining immunotherapy applications. Identifying biomarkers enables the selection of patients who are more likely to respond positively to immunotherapy, whereas understanding resistance mechanisms is key to addressing the current constraints of immunotherapy and enhancing its overall success.

In thyroid cancer research, the presence of tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, is closely related to patient prognosis. Studies have shown that in differentiated thyroid cancer (DTC), the degree of CD8+ T cell infiltration is significantly correlated with prolonged overall survival in patients. Specifically, when there is a high density of CD8+ T cell infiltration in DTC tumor tissues, patients tend to exhibit longer survival times, suggesting the important role of immune cells in the progression of thyroid cancer and the potential for improving prognosis through immunotherapy (Kim et al., 2018). In contrast, anaplastic thyroid cancer (ATC) presents a highly immunosuppressive microenvironment. In this environment, the number of regulatory T cells (Tregs) and tumor-associated macrophages (TAMs) significantly increases. These immune cells typically have immunosuppressive effects, thereby facilitating tumor cell escape and progression. Therefore, the microenvironment characteristics of ATC pose new challenges for immunotherapy, necessitating the development of more effective strategies to overcome this immunosuppressive state (Landa et al., 2021).

In the study of thyroid cancer, the involvement of tumor-infiltrating lymphocytes (TILs), especially CD8+ T cells, plays a significant role in determining patient outcomes. Research indicates that in cases of differentiated thyroid cancer (DTC), the extent of CD8+ T cell presence within tumors is strongly linked to improved patient survival rates. Notably, a higher concentration of CD8+ T cells within DTC tumor tissues is associated with better survival outcomes, highlighting the critical influence of immune cells on the disease's progression and the promising impact of immunotherapy on enhancing patient prognosis (Kim et al., 2018). On the other hand, anaplastic thyroid cancer (ATC) is characterized by a notably suppressive immune environment. This setting sees a marked rise in the

population of regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), both known for their roles in dampening immune responses, thus aiding in the evasion and advancement of tumor cells. The distinct immune landscape of ATC introduces additional hurdles for immunotherapy, underscoring the need for innovative approaches to counteract the immunosuppressive conditions prevalent in ATC (Landa et al., 2021).

2. CLINICAL PRACTICE OF IMMUNOTHERAPY STRATEGIES

2.1 Immune Checkpoint Inhibitors

Immune checkpoint inhibitors restore and enhance anti-tumor immune responses by blocking key pathways through which tumor cells evade immune system surveillance. In the treatment of thyroid cancer, PD-1/PD-L1 inhibitors and CTLA-4 inhibitors are two major types of immune checkpoint inhibitors.

2.1.1 PD-1/PD-L1 Inhibitors

KEYNOTE-028 Trial: This study assessed the effectiveness of Pembrolizumab, a PD-1 inhibitor, in individuals with advanced thyroid cancer expressing PD-L1. The findings revealed an objective response rate (ORR) of 9%, suggesting that a subset of patients with advanced thyroid cancer may benefit from PD-1 inhibitor treatment, despite the modest response rate (Mehnert et al., 2019). NCT03246958 Trial: This trial investigated the combination of Atezolizumab, a PD-L1 inhibitor, and Cobimetinib, a MEK inhibitor, in treating anaplastic thyroid cancer (ATC). The combination yielded an ORR of 25%, outperforming historical controls and offering a promising therapeutic approach for ATC patients (Wirth et al., 2022).

2.1.2 CTLA-4 Inhibitor

Ipilimumab is a CTLA-4 inhibitor with limited efficacy as a monotherapy for thyroid cancer. However, studies have shown that combining Ipilimumab with radiotherapy can enhance local control rates, offering a new approach for local treatment of thyroid cancer (Romano et al., 2020).

2.2 Adoptive Cell Therapy

Adoptive cell therapy involves extracting immune cells from a patient, modifying and amplifying them in the lab, and then reintroducing them to attack cancer cells. In thyroid cancer, two key approaches under this umbrella are CAR-T cell therapy and TIL therapy. Early research on CAR-T cells targeting the thyroid-stimulating hormone receptor (TSHR) has shown promising results in suppressing tumor growth in thyroid cancer models, highlighting a potential new direction for CAR-T therapy in this area (Li et al., 2021). Additionally, a phase I clinical trial investigating TIL therapy in advanced anaplastic thyroid cancer (ATC) reported that one patient achieved partial tumor shrinkage, suggesting TIL therapy may hold promise for ATC treatment (Tran et al., 2022).

2.3 Cancer Vaccines

Cancer vaccines aim to induce a specific immune response against tumor cells in a patient's own immune system, thereby treating the tumor. In the treatment of thyroid cancer, individualized vaccines based on neoantigens are a promising type of cancer vaccine. Individualized Vaccines Based on Neoantigens: Studies have shown that individualized vaccines based on neoantigens can induce antigen-specific T-cell responses in patients with differentiated thyroid cancer (DTC), thereby enhancing anti-tumor immune responses. This finding provides a new basis for the application of cancer vaccines in thyroid cancer (Ott et al., 2020).

3. BIOMARKERS AND PREDICTION OF THERAPEUTIC EFFICACY

In assessing the effectiveness of immunotherapy, especially immune checkpoint inhibitors (ICIs), in thyroid cancer, scientists have pinpointed several biomarkers that may impact patient outcomes. Notably, tumor mutation burden (TMB), microsatellite instability (MSI) status, and gene fusion events have emerged as critical factors receiving considerable focus in recent research. High Tumor Mutation Burden (TMB): TMB measures the number of mutations per million base pairs (Mb) in the coding regions of a tumor's genome. Research indicates that tumors with high TMB (generally defined as TMB $\geq$ 10 mut/Mb) tend to produce more tumor-specific antigens, which can trigger a robust immune response against the cancer. Consequently, patients with high TMB tumors often show better responses to ICIs. A study by Goodman et al. highlighted that thyroid cancer patients with high TMB had a

threefold higher response rate to ICIs, underscoring TMB's role as a predictive biomarker for ICI efficacy (Goodman et al., 2021).

Microsatellite Instability (MSI) refers to alterations in the length of microsatellite sequences within the tumor genome, often caused by defects in DNA mismatch repair. Tumors with high microsatellite instability (MSI-H) tend to have greater immunogenicity due to the presence of more mutations and abnormal DNA repair products, which can act as immune system targets. However, the connection between MSI status and the effectiveness of immune checkpoint inhibitors (ICIs) in thyroid cancer remains unclear, as thyroid cancer is not typically classified as an MSI-H tumor. Nonetheless, as research progresses, future studies may uncover more links between MSI and immune therapy responses in thyroid cancer. Gene fusion events are another significant genetic alteration in thyroid cancer, with RET/PTC rearrangements being particularly notable. These rearrangements are commonly found in papillary thyroid cancer (PTC) and can lead to abnormal expression and functional changes in the RET protein. A study by Prete et al. revealed that RET/PTC rearrangements might enhance the expression of major histocompatibility complex I (MHC-I), thereby increasing tumor immunogenicity (Prete et al., 2022). MHC-I plays a crucial role in presenting tumor-specific antigens to T cells, initiating an anti-tumor immune response. Thus, RET/PTC rearrangements could potentially improve patient sensitivity to ICIs through this mechanism. In summary, tumor mutational burden (TMB), MSI status, and gene fusion events are key factors influencing the response of thyroid cancer patients to ICIs. As research on these biomarkers advances, more precise and effective immunotherapy strategies may emerge, ultimately enhancing treatment outcomes and survival rates for thyroid cancer patients.

4. CHALLENGES AND FUTURE DIRECTIONS

4.1 Mechanisms of Drug Resistance

Despite some encouraging progress in the field of immunotherapy for thyroid cancer, numerous challenges remain. Immunotherapy, particularly immune checkpoint inhibitor (ICI) therapy, has shown significant efficacy in thyroid cancer; however, some patients still develop resistance. Understanding the mechanisms of drug resistance is crucial for optimizing treatment strategies.

IFN-γ is an important cytokine in the immune system that plays a pivotal role in activating immune responses and inhibiting tumor growth. However, some studies have suggested that the loss of the IFN-γ signaling pathway in thyroid cancer may be a significant reason for patients' resistance to ICIs (Garcia-Diaz et al., 2020). This loss may enable tumor cells to evade the surveillance and attack of the immune system, allowing them to continue to grow and spread. The upregulation of immunosuppressive cytokines is also a key factor contributing to resistance to immunotherapy. For example, cytokines such as IL-10 and TGF-β can inhibit the activation and proliferation of immune cells, thereby reducing the antitumor capability of the immune system (Cunha et al., 2022). In thyroid cancer, the upregulation of these cytokines may allow tumor cells to survive and continue to proliferate under the pressure of the immune system.

4.2 Combined Therapy Strategies

To address immunotherapy resistance, scientists are investigating various combination therapies to enhance effectiveness and minimize adverse effects. Targeted therapy involves drugs that focus on specific molecular markers in cancer cells, blocking their growth and spread. Combining immune checkpoint inhibitors (ICIs) with targeted agents, such as BRAF/MEK inhibitors, can amplify the immune system's ability to fight tumors, potentially improving outcomes. This approach has shown promise in several cancers and may hold significant potential for thyroid cancer treatment in the future. Epigenetic modulators, which influence gene expression without changing DNA sequences, are another area of interest. Histone deacetylase (HDAC) inhibitors, a type of epigenetic modulator, work by increasing gene expression through the inhibition of HDAC activity. Research indicates that HDAC inhibitors can boost the ability of tumor cells to present antigens, thereby strengthening the immune system's response to cancer (Ferrari et al., 2021). As a result, pairing HDAC inhibitors with ICIs could offer a promising strategy to enhance therapeutic effects and lower the likelihood of resistance.

5. CONCLUSION

Immunotherapy offers a new option for advanced thyroid cancer, but it is necessary to screen for beneficiary populations using biomarkers and optimize combination therapy regimens. Thyroid cancer, especially advanced

and anaplastic thyroid cancer (ATC), still lacks effective treatment options, but immunotherapy brings new hope. This article reviews the clinical progress of immunotherapy strategies such as immune checkpoint inhibitors (ICIs), adoptive cell therapy (ACT), and tumor vaccines in thyroid cancer, and discusses related biomarkers, predictive factors for efficacy, as well as the challenges and future directions. More phase II/III clinical trials are needed to verify long-term efficacy in the future. Immunotherapy shows great potential in thyroid cancer, but further research and optimization are required to improve efficacy and overcome resistance. In the future, with a deeper understanding of the immune mechanisms of thyroid cancer and the continuous emergence of new immunotherapy technologies, we believe that immunotherapy will bring benefits to more patients with thyroid cancer.

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