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Advances in immunotherapy for HNSCC

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ABSTRACT

Head and Neck Squamous Cell Carcinoma (HNSCC) is a cancer that originates in the mucosal surfaces of the head and neck, including the mouth, throat, and larynx. Immunotherapy has emerged as a promising treatment for HNSCC, especially for patients whose cancers are resistant to traditional therapies such as surgery, radiation, and chemotherapy. In this minireview article, we summarized the role of immunotherapy in HNSCC. Checkpoint inhibitors are a class of immunotherapy that work by blocking certain proteins that suppress the immune system's ability to attack cancer cells. In HNSCC, the most studied checkpoint inhibitors are PD-1/PD-L1 Inhibitors. These include drugs like Pembrolizumab (Keytruda) and Nivolumab (Opdivo). PD-1 is a protein on immune cells that, when engaged by its ligands (PD-L1 on cancer cells), dampens the immune response. Blocking PD-1 helps reactivate the immune system to recognize and destroy cancer cells. Drugs like Atezolizumab (Tecentriq) target the PD-L1 protein, which is often upregulated in cancer cells to escape immune surveillance. By blocking PD-L1, these drugs prevent cancer cells from evading the immune system. These checkpoint inhibitors have shown efficacy in advanced or recurrent HNSCC, particularly in patients whose tumors express PD-L1. Combination strategies that combine immunotherapy with other treatments, such as chemotherapy, radiation therapy, or targeted therapy, are also being explored to enhance the effectiveness of immunotherapy in HNSCC. These combinations can help overcome resistance mechanisms and potentially improve outcomes. Chemotherapy may induce immune-stimulatory effects, making the tumor more sensitive to immunotherapy. Radiation can induce "immunogenic cell death," releasing tumor antigens that can enhance the immune system's response to the cancer when combined with checkpoint inhibitors. While immunotherapy has shown promising results in treating HNSCC, several challenges remain. For example, not all tumors respond equally to immunotherapy, and some cancers develop resistance over time. Tumors can create a microenvironment that suppresses immune activity, making it difficult for immunotherapies to work effectively. Immune-related side effects, such as inflammation or autoimmunity, can occur with checkpoint inhibitors.

Research continues into refining biomarkers for patient selection, optimizing combination therapies, and finding ways to overcome resistance. In conclusion, immunotherapy represents a major advancement in the treatment of HNSCC, offering new hope for patients with advanced or recurrent disease. Ongoing research is focusing on improving the efficacy, safety, and applicability of these therapies, with the goal of enhancing patient outcomes and expanding their use across different subtypes of HNSCC.

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1. Introduction

At present, the treatment of patients with locally advanced head and neck squamous cell carcinoma (HNSCC) is still a surgery-based comprehensive treatment. Despite aggressive anti-tumor therapy, about 50% of patients develop recurrence, greatly affecting the survival of patients. The 5-year overall survival rate of patients with advanced HNSCC is about 50%. Once patients develop relapse, the 1-year survival rate is about 15%, with a median survival time of 10-14 months [1]. An increasing number of studies have shown that the immune system plays a key role in the development of HNSCC and that HNSCC cells express inhibitory immune checkpoint molecules to escape immune surveillance. With the advent of immunotherapy, the application of immune checkpoint inhibitors (ICIs) has changed the mode of systemic anti-tumor therapy in relapsed and metastatic HNSCCs, showing better efficacy and safety in both platinum-resistant and -sensitive patients. By summarizing the immune checkpoints in HNSCC, we elaborated on the immune combination treatment scheme in preclinical studies and explored the application prospect of immunotherapy as neoadjuvant therapy in HNSCC.

2. Immune checkpoint in HNSCC

With a deep understanding of the interaction between the tumor immune microenvironment (TIME) and immunotherapy, the role of immunomodulators in HNSCC therapy has gradually attracted people's interest, among which T cell activation and immune checkpoint molecules are crucial for the occurrence of anti-tumor immune response. During HNSCC development, T cell activation is inhibited by several pathways, usually by the expression of certain ligands on tumor cells or antigen-presenting cells (PD-L1/2, CD80/CD86, Galectin-9, Lectin/FGL1, CD155/GITRL and VSIG-3), which bind to the receptors on T cells (PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, GITR and VISTA) and inhibit the activation and the anti-tumor function of T cells [2].

As the first immune checkpoint receptor for clinical application, CTLA-4 is mainly expressed on the surface of T cells, but less so in monocytes, neutrophils, and dendritic cells [3]. CTLA-4 is also expressed on the surface of Treg cells and produces the immunosuppressive molecule TGF-β when activated by CD28, thereby inducing T-cell depletion, and inhibiting the immune response [4]. Anti-CTLA-4 mAb is mainly Ipilimumab and Temelimab, which are now approved by the FDA for the treatment of patients with metastatic malignant melanoma. A phase-I clinical trial evaluating the efficacy and safety (NCT01935921) of Ipilimumab plus anti-EGFR therapy and radiotherapy in patients with locally advanced HNSCC showed that the 3-year disease-free and overall survival rate of HNSCC patients was 72% (90% CI, 57%-92%) and 72% (90% CI, 56%-92%), respectively, without significant immune-related toxicity [5].

Monoclonal PD-1/PD-L1 antibody therapy against the T cell immune checkpoint is currently the most promising immunotherapy modality. By binding to PD-1 on the surface of T cells or PD-L1 ligand on the surface of tumor cells, it blocks intercellular PD-1/PD-L1 communication and relieves T cell inhibition, thus exerting an anti-tumor immune response effect [6]. In 2016, the US Food and Drug Administration (FDA) approved anti-PD-1 Nivolumab and Pembrolizumab to treat HNSCC patients with platinum-resistant relapse, marking the entry of the era of anti-tumor immunotherapy for HNSCC [7]. In 2019, Pembrolizumab was approved for first-line antitumor therapy in HNSCC patients.

Although ICIs targeting PD-1 and its ligand PD-L1 have been approved for anti-tumor immunotherapy of a variety of malignant tumors, including melanoma, non-small cell lung cancer (NSCLC), mismatch repair defect/microsatellite unstable colorectal cancer, triple-negative breast cancer, liver cancer and HNSCC, we still face many challenges to further improve the anti-tumor immune response rate and response time of patients due to the existence of innate resistance and acquired resistance.

3. Combination therapy of ICIs in HNSCC

At present, most HNSCC patients are diagnosed with advanced local diseases, in addition to traditional radiotherapy, chemotherapy, and targeted therapy, immunotherapy with its high specificity, and low side effects, completely changed the platinum-refractory recurrent or metastatic (R/M) HNSCC treatment status, becoming the development trend of HNSCC treatment. In R/M HNSCC patients, about 13% -18% of patients developed an immune response to anti-PD-1 monotherapy [8]. Although anti-tumor immunotherapy, especially ICIs against PD-1 and its ligand PD-L1, including Nivolumab, Pembrolizumab, and Durvalumab, have shown good efficacy in HNSCC patients, they showed limited efficacy. The objective response rate (ORR) with monotherapy

was less than 20% in clinical trials, including KEYNOTE-012 [9], KEYNOTE-040 [10], KEYNOTE-055 [11], CheckMate-141 [12], KEYNOTE-048 [13]. The ORR in China was 18%, 14.6%, 16%, 13.3%, and 16.9%, respectively. Currently, combinational treatment options are actively explored in HNSCC including dual-free combination, target-free combination, and ICI's combination with chemoradiotherapy.

3.1 Double-free combination

PD-1/PD-L1 inhibitors are effective in multiple cancer species. However, recent studies have found an elevated expression of other immune checkpoint molecules during anti-PD-1/PD-L1 mAb therapy, leading to the development of acquired resistance. Therefore, multiple preclinical studies and clinical trials are actively exploring the prospect of dual-free combination regimens in anti-tumor immunotherapy.

Among them, a representative dual-free combination treatment regimen is anti-PD-1 mAb combined with anti-CTLA-4 mAb. Blocking CTLA-4 induces memory T cell proliferation, while the PD-1 mAb is involved in the regulation of T cell and NK cell functions [14, 15]. There are several clinical trials in HNSCC, a phase III clinical trial comparing the efficacy of anti-CTLA-4 mab (Ipilimumab) with anti-PD-1 mab (Nivolumab) with the standard treatment EXTREME, exploring the possibility of first-line therapy in R/M HNSCC patients (NCT02741570). A phase I clinical trial found a higher combination ORR in PD-L1-negative H NSCC patients (27% vs 5%), suggesting that patients with lower PD-L1 expression may benefit from this regimen. In addition, a non-randomized phase Ib/IIa clinical trial evaluated the possibility of using this combination regimen as a neoadjuvant therapy in HNSCC patients (NCT03003637). The results showed a major pathological response rate (MPR) in HNSCC patients receiving combination therapy 35%, vs 17% of the patients in the Nivolumab monotherapy group. Meanwhile, no recurrence was observed in HNSCC patients achieving the MPR objective. These results suggest that Ipilimumab combined with Nivolumab is safe and effective as neoadjuvant therapy in patients with HNSCC [16].

3.2 Target-free combination

Many studies have revealed the specific molecular mechanisms regulating complex TIME in HNSCC. Inhibition of related signaling pathways can synergistically sensitize the efficacy of HNSCC immunotherapy. Phase Ib and II clinical trials are actively exploring the efficacy of anti-EGFR therapy in combination with immunotherapy in locally advanced HNSCC. A phase II single-arm clinical study ALPHA (NCT03695510) evaluated the efficacy of EGFR-TKI Afatinib combined with Pembrolizumab in patients with platinum-resistant R/M HNSCC. The results showed that the ORR was 41.1% with a median survival time of 8.9 months. Gene expression analysis found an improved antigen presentation process in patients treated with the combination regimen [17].

3.3 Immunotherapy combined with chemoradiation

In the process of treatment selection for locally advanced HNSCC patients, the key factor is to integrate adequate immunotherapy into standard therapy because the standard treatment regimen has both activating and inhibiting immune response effects [18].

Radiotherapy is an important treatment option for locally advanced HNSCC. Recent studies showed that radiotherapy affected the anti-tumor immune response of HNSCC by inducing multiple biological effects on tumor cells [19, 20]. In addition to a direct effect on tumor cells in the target areas, radiotherapy elicited an anti-tumor immune response in the adjacent non-target cells by promoting the expression of inflammatory and immunomodulatory factors [21]. It has been shown that radiotherapy improves the killing ability of TILs on tumor cells by promoting the expression of MHC-I/II. In addition, radiotherapy promoted the expression of pro-inflammatory factors such as TNF, ICAM-1, and GM-SGF by activating NF-κB, and elevated levels of inflammatory factors including IL-6 and IL-8 were found in HNSCC patients receiving chemoradiotherapy [22]. On the other hand, radiation therapy induces danger signals by necrotic cells, mainly heat shock protein 70 (HSP70) and high-mobility protein High mobility Group Box-1 (HMGB-1), and activated antigen-presenting cells (APC), thus improving the innate immune response [21]. However, as found in animal tumor models, radiotherapy promoted PD-L1 expression, thereby inhibiting the cellular immune response of effector T cells to tumors [23].

Studies also showed that systemic chemotherapy not only has direct cytotoxic effects on tumor cells but also exerts anti-tumor immune response by modulating host innate and adaptive immune responses [24]. Combining immunotherapy with chemotherapy showed higher safety and efficacy as first-line therapy compared with chemotherapy alone. The chemo-

therapy for HNSCC is a platinum-based regimen. Platinum drugs can regulate the anti-tumor immune response: i) disrupt the function of tumor-associated macrophages (TAMs), and a preclinical study found that ovarian cells co-cultured with TAMs are more sensitive to platinum [25]; ii) inhibit bone marrow-derived suppressor cells (Myeloid-Derived Suppressor Cells, MDSCs) to promote the anti-tumor immune response; iii) promote the T cell-mediated immune response and TILs infiltration by enhancing the release of IL-2 and IFN-γ [26]. In platinum-treated tumor cells, inhibition of PD-L1 expression improves the ability of T cells to recognize and kill tumor cells [27].

4. Research status of neoadjuvant immunotherapy in HNSCC

In recent years, studies have been actively exploring the potential of ICIs as neoadjuvant therapy. In addition, another key reason to advocate the early use of anti-tumor immunotherapy is the hope to achieve reactivation of anti-tumor immune response before immune depletion. This intensive treatment is more important for HPV-negative HNSCC patients because this group of patients has a higher risk of recurrence and worse prognosis compared with HPV-positive HNSCC patients. Patients with HPV-negative HNSCC are more likely to benefit from neoadjuvant HNSCC immunotherapy compared with HPV-positive patients [28, 29]. These studies encourage clinical researchers to design rational clinical trials to explore the possibility of anti-tumor immunotherapy as a neoadjuvant therapy.

Several single-arm clinical studies have been conducted to evaluate the role of anti-PD-1 mAb and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) as neoadjuvant therapy in locally advanced HNSCC. About 22% of high-risk HNSCC patients had a pathological remission rate of about 50%, and a 1-year recurrence rate of 16.7% without serious adverse reaction events and surgical delays, which is significantly lower than the historical recurrence rate of 35% [29]. Interestingly, the anti-tumor effect was achieved with doubled MPR even when patients only received Pembrolizumab monotherapy two weeks before the surgery [30]. However, it is unclear whether the benefit was a prolonged treatment and efficacy assessment interval or a second course of treatment. Recently reported the results of clinical trials to evaluate Pembrolizumab as neoadjuvant therapy in 92 HPV-negative locally advanced HNSCC showed a significant improvement in one-year disease-free survival (DFS) in patients achieving partial response compared with patients without immune response (93% vs 72%, HR = 0.29) [31]. Based on this clinical outcome, another new clinical trial Keynote-689 (NCT03765918) will evaluate the efficacy and safety of Pembrolizumab plus standard radiotherapy regimen (regardless of platinum therapy history) in patients with locally advanced HNSCC. It is necessary to further explore the efficiency of the anti-tumor immune response of ICIs in combination with other therapeutic options such as neoadjuvant therapy in HNSCC.

A single-center randomized clinical study was conducted on 29 patients with oral cancer to compare the efficacy of Nivolumab monotherapy and its combination with Ipilimumab as neoadjuvant therapy. The results showed that none had delayed surgery, one Nivolumab monotherapy, and three patients with combinational therapy had an MPR of more than 90% [32]. Another clinical study evaluated the efficacy of Nivolumab monotherapy and its combination with Ipilimumab as neoadjuvant therapy. The study found that about 17% of Nivolumab monotherapy and 35% of HNSCC patients with Nivolumab plus Ipilimumab achieved more than 90% of MPR. More importantly, none of the patients who achieved MPR had recurrence during 2 years of follow-up [16].

Some immune activators were also combined with ICIs as a neoadjuvant regimen in patients with locally advanced HNSCC. Sitravatinib is a tyrosine kinase receptor inhibitor (TKI) for multiple targets, including TYRO3, AXL, MERTK, and VEGF family receptors. It has immunostimulatory activity by activating M1 macrophages while simultaneously inhibiting MDSC function. It has been shown that combining Sitravatinib with Nivolumab had better efficacy, nine of the 10 patients achieved pathological downstaging with a good tolerance (NCT03575598). During the subsequent postoperative follow-up of 21 months, none of the patients developed a recurrence [33]. Combined with Nivolumab and the NK cell immune checkpoint inhibitor Lirilumab (anti-KIR2D mAb) reduced tumors by over 50% in 43% of HNSCC patients with good safety [34].

Immunotherapy combined with chemotherapy improved the efficiency of anti-tumor response in patients, but the incidence of adverse reactions was also increased. A phase II clinical study with Nivolumab plus Carboplatin plus Paclitaxel as a neoadjuvant regimen showed 37% had immune-related adverse

events above G2 (irAEs), although an MPR of 69% was reported in 27 patients with locally advanced HNSCC.

Immunotherapy combined with targeted therapy showed promising outcomes in patients with locally advanced HNSCC. ICIs in combination with poly ADP-ribose polymerase inhibitors (PARPi) exerted synergistic effects by activating the STING pathway and promoting TILs [35]. Preclinical studies and clinical trials have evaluated the efficacy of ICIs combined with PARPi in different malignancies including HNSCC, regardless of BRCA mutation, PD-L1 status, or previous platinum-based antitumor therapy [36]. A phase II clinical study is recruiting subjects to evaluate the efficacy of Pembrolizumab in combination with PAPRi (Olaparib) as neoadjuvant therapy in patients with locally advanced HNSCC (NCT 05366166).

5. Outlook

With the in-depth study and exploration of intercellular communication and signaling pathways between immune cells and tumor cells, it is promising to imply anti-tumor immunotherapy in HNSCC. Although ICI monotherapy and combination therapy can improve the prognosis of HNSCC patients, many immunotherapy regimens take a long time to achieve clinical immune response and may even have pseudo-progression. Therefore, during preclinical studies and clinical trials, experimental schemes should be rationally designed to fully consider the potential immune-related adverse reactions of different combination schemes and to ensure patients complete treatment. Moreover, biomarkers assessing the efficacy of immunotherapy should be explored to promote the implementation of individualized diagnosis and treatment for HNSCC.

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