

Advances in Neoadjuvant and Combination Therapies for Locally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract: Current treatment modalities for locally advanced head and neck squamous cell carcinoma (HNSCC) are increasingly diverse. The CSCO guidelines for head and neck cancer diagnosis and treatment indicate that neoadjuvant therapy followed by radical surgery has become one of the recommended treatment strategies. In recent years, immune checkpoint inhibitors (ICIs) have been discovered and applied in the treatment of locally advanced HNSCC, achieving promising results. Most patients receiving ICI monotherapy or ICI combined with targeted or chemotherapeutic agents for 2-4 cycles demonstrate improved event-free survival (EFS), major pathological response (MPR) rates, clinical complete response (CR) rates, and partial response (PR) rates. Additionally, these regimens significantly help control adverse reactions. Given the heterogeneity of the tumor microenvironment across individual patients, selecting the most suitable personalized treatment plan from various options is a current research priority. This article analyzes neoadjuvant strategies involving upfront systemic therapy for locally advanced HNSCC, exploring the sequence of different agents and subsequent treatment plans.

Keywords: Neoadjuvant Therapy; Immunotherapy Combination Therapy; Chemotherapy; Targeted Therapy; Locally Advanced Head and Neck Squamous Cell Carcinoma.

1. Introduction

Globally, there are over 900,000 new cases of head and neck squamous cell carcinoma (HNSCC) and approximately 400,000 deaths annually. Based on clinical staging, patients with stage I and II HNSCC typically achieve favorable prognoses following primary surgical intervention[1]. However, a significant proportion of patients present with locally advanced disease at diagnosis. These patients have extensive lesions, and surgery alone is often associated with prolonged operation times, larger resection volumes, potential total organ removal, significant trauma, and poorer post-operative quality of life [2].

The introduction of immune checkpoint inhibitors (ICIs) into clinical practice and their application for locally advanced HNSCC has changed the treatment landscape. The use of PD-1 inhibitors enables tumor volume reduction, shrinkage or even elimination of primary lesions, leading to clinical and even pathological complete response (pCR) in many patients[3]. The KEYNOTE-048 study reported a median overall survival of 13.0 months for patients treated with pembrolizumab combined with chemotherapy. Most treated patients experience clinical downstaging and delayed disease progression[4]. Nonetheless, some patients show little to no clinical response or even experience disease progression. Therefore, identifying which patient populations benefit most from specific neoadjuvant regimens is a critical research focus.

2. Exploration of Neoadjuvant Immunotherapy Monotherapy

Neoadjuvant immunotherapy works by restoring the body's immune response against tumor cells. The human immune system possesses a "surveillance" function, capable of

recognizing abnormally proliferating or metabolizing cells. However, tumor cells employ various mechanisms to evade immune detection, allowing uncontrolled growth [5]. ICIs block inhibitory immune checkpoint pathways, enabling immune cells to recognize tumor cells again and restoring immune-mediated killing. Programmed death-1 (PD-1) is a key immunosuppressive transmembrane protein on T cells, whose ligand is PD-L1[6]. Tumor cells expressing PD-L1 bind to the PD-1 receptor on T lymphocytes, recruiting the tyrosine phosphatase SHP-2 to the PD-1 cytoplasmic domain. This leads to dephosphorylation of T-cell receptor (TCR) signaling molecules, dampening downstream signals, reducing T-cell activation, and facilitating immune escape[7]. Anti-PD-1/PD-L1 monoclonal antibodies block this pathway, preventing the inhibition of T-cell activation, allowing sustained TCR signaling, and enabling effective tumor cell recognition and elimination. PD-L1 expression levels, assessed by Tumor Proportion Score (TPS) or Combined Positive Score (CPS), correlate with treatment efficacy. Studies indicate patients with CPS ≥ 1 or TPS $\geq 50\%$ show significantly improved objective response rates [8].

Currently, in China, PD-1/PD-L1 inhibitor monotherapy may be considered for patients with recurrent/metastatic (R/M) HNSCC who have an ECOG performance status ≥ 2 and no contraindications to immunotherapy [8].

However, treatment outcomes vary significantly among specific patient subgroups [9]. Some literature suggests monotherapy carries a lower risk of surgery delay, but efficacy differs greatly, particularly in HPV-associated cancers, where responses are less stable[10]. HPV-negative patients may exhibit quicker immune responses, potentially due to stronger immunogenic tumor-related viral neoantigens and a more active intratumoral immune microenvironment [11].

3. Exploration of Neoadjuvant Immunotherapy Combined with Chemotherapy

A study investigating toripalimab (an anti-PD-1 antibody) combined with gemcitabine and cisplatin as neoadjuvant therapy for locally advanced HNSCC reported no surgery delays. Patients achieved pathological and clinical complete responses, with an MPR rate of 27.8% and a pCR rate of 16.7%[12]-[14]. Compared to MPR (9.7%) and pCR (2.9%) rates with immunotherapy monotherapy, combination with chemotherapy yields superior outcomes[15]. Another domestic study on resectable oral squamous cell carcinoma (OSCC) used toripalimab combined with nab-paclitaxel and cisplatin on a 21-day cycle. After two cycles, the MPR rate reached 60%, and the clinical downstaging rate exceeded 50%[16]. With a two-year follow-up, the disease-free survival (DFS) rate was as high as 90%. This suggests chemotherapy promotes antigen release and stimulates T-cell activation, potentially enhancing immunotherapy efficacy. Regarding sequence, some research indicates administering the immune checkpoint inhibitor first might be more effective, as subsequent chemotherapy could reduce the expanded T-cell population activated by PD-1 blockade, diminishing the treatment effect[17].

4. Exploration of Neoadjuvant Immunotherapy Combined with Targeted Therapy

Expert consensus on ICIs for R/M HNSCC suggests that for patients unsuitable for chemotherapy or anti-PD-1 monotherapy, combinations like pembrolizumab or nivolumab with anti-EGFR monoclonal antibodies (e.g., cetuximab) can be considered as first or later-line treatment[18]. EGFR is a protein expressed on normal epithelial and many cancer cells, transmitting growth and proliferation signals upon ligand binding. EGFR monoclonal antibodies bind specifically to cancer cell surfaces, blocking these growth signals. Most literature supports the synergistic effect of combining targeted and immunotherapeutic agents[19]. Anti-EGFR antibodies not only directly inhibit tumor growth but also modify the tumor microenvironment, facilitating immune cell (especially T-cell) infiltration and tumor recognition[20]-[21]. In healthy individuals, regulatory T cells (Tregs) maintain immune balance by suppressing excessive activation of other immune cells, a mechanism known as immune checkpoint regulation[22]. Targeted agents like cetuximab may help "release the brake" applied by checkpoints like PD-1, enhancing the ability of T cells to identify and eliminate tumor cells[23].

5. Summary

Immunotherapy has become a hotspot in HNSCC research. Neoadjuvant immunotherapy shows promise even for resectable HNSCC, while combinations with chemotherapy or targeted therapy represent breakthroughs in R/M HNSCC. Studies suggest that patients at initial diagnosis often have better immune function and greater tumor antigen exposure. Neoadjuvant immunotherapy can induce broad immune responses, and resident memory T cells may help eliminate residual tumor cells post-surgery, providing a rationale for perioperative immunotherapy. Several phase I/II trials

demonstrate that anti-PD-1 inhibitors, alone or combined with chemotherapy, achieve promising pathological response rates and progression-free survival in the neoadjuvant setting with acceptable safety profiles. Neoadjuvant therapy can downstage tumors, but whether this allows for safely reduced surgical margins requires further investigation.

In conclusion, research on neoadjuvant immunotherapy and combination therapies for locally advanced HNSCC opens new avenues for perioperative immunotherapeutic interventions.

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