Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(5), 06-09 | ISSN:2251-6727

Novel Immunotherapeutic Approaches for Head and Neck Squamous Cell Carcinoma: A Paradigm Shift in Treatment

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(Received: 16 July 2025 Revised: 20 August 2025 Accepted: 02 September 2025)

KEYWORDS

Cancer, Cancer Vaccines, Immune Checkpoint Inhibitors, Immunotherapy , Squamous Cell Carcinoma

ABSTRACT:

Head and neck squamous cell carcinoma (HNSCC) remains a major global health challenge, with high morbidity and mortality rates despite advances in treatment. Conventional therapies such as surgery, radiation, and chemotherapy provide limited long-term benefits due to recurrence and resistance. Immunotherapy has emerged as a promising alternative, leveraging the body's immune system to target malignant cells. This review explores the principles, mechanisms, and current therapeutic strategies in immunotherapy for HNSCC, including immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines. Challenges, ongoing clinical trials, emerging biomarkers, and future directions in the field are also discussed.

1. Introduction

Head and neck cancers (HNC) are a heterogeneous group of malignancies arising from the mucosal surfaces of the upper aerodigestive tract. HNSCC accounts for approximately 90% of all HNCs, with tobacco and alcohol use being the primary risk factors [1]. Additionally, human papillomavirus (HPV) has been implicated in a subset of cases, particularly in oropharyngeal carcinomas [2]. The prognosis for advanced HNSCC remains poor, necessitating the exploration of novel therapeutic strategies such as immunotherapy [3].

Despite conventional treatment options such as surgery, radiotherapy, and chemotherapy, the overall survival rates for patients with advanced HNSCC remain low. The high recurrence rates and drug resistance have prompted researchers to explore immunotherapy, a novel approach that leverages the body's immune system to target and eliminate cancer cells [4]. This review provides an in-depth analysis of the role of immunotherapy in HNSCC, focusing on its mechanisms, clinical applications, emerging therapies, and future directions.

2. The Immune System and Cancer

The immune system plays a dual role in cancer progression. While immune surveillance can eliminate tumor cells, certain tumors develop mechanisms to evade immune detection. This process, known as tumor immunoediting, involves three phases: elimination, equilibrium, and escape [5]. The tumor microenvironment (TME) fosters immune evasion through various mechanisms, including suppression of antigen presentation, recruitment of regulatory immune cells, and expression of immune checkpoint molecules [6].

3. Tumor Microenvironment (TME) and Immune Escape

The TME is composed of immune cells, stromal cells, and extracellular matrix components that collectively contribute to cancer progression and immune evasion

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www.jchr.org
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[7]. Tumors can manipulate the immune response by promoting an immunosuppressive microenvironment. Regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) play critical roles in dampening anti-tumor immunity [8]. Additionally, tumors can upregulate immune checkpoint molecules such as PD-L1 and CTLA-4 to evade immune surveillance [9].

Understanding these mechanisms is essential for developing effective immunotherapies. Emerging research suggests that targeting components of the TME can enhance the efficacy of existing immunotherapies. Strategies such as combining checkpoint inhibitors with TME-modulating agents are being explored to improve therapeutic outcomes [10].

4. Immunotherapy Approaches in HNSCC

a. Immune Checkpoint Inhibitors (ICIs)

Immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) regulate immune responses to prevent excessive activation [11]. Tumors exploit these pathways to evade immune attacks. ICIs, including pembrolizumab and nivolumab, target PD-1/PD-L1 interactions, restoring T-cell activity against tumors [12]. Clinical trials have demonstrated improved overall survival in patients with recurrent or metastatic HNSCC treated with ICIs compared to standard chemotherapy [13].

Despite promising results, not all patients respond to checkpoint inhibition therapy. The response rates vary, with some tumors exhibiting resistance due to the absence of sufficient tumor-infiltrating lymphocytes (TILs) or the presence of alternative immunosuppressive pathways [14]. Ongoing research is focused on identifying biomarkers that can predict response to ICIs and exploring combination therapies to enhance their efficacy [15].

b. Biomarkers for Predicting Response to ICIs

Biomarkers play a crucial role in patient selection for immunotherapy. High PD-L1 expression has been correlated with better responses to checkpoint inhibitors [16]. Additionally, tumor mutational burden (TMB), microsatellite instability (MSI), and immune gene signatures are being investigated as potential predictive biomarkers [17]. Ongoing studies aim to establish reliable biomarkers to guide treatment decisions and improve patient outcomes [18].

c. Adoptive Cell Therapy (ACT)

Adoptive cell therapy involves the extraction and modification of a patient's immune cells to enhance their tumor-targeting capabilities [19]. Chimeric antigen receptor (CAR) T-cell therapy has shown promise in hematologic malignancies, though its efficacy in solid tumors like HNSCC remains under investigation [20]. Other ACT strategies include tumor-infiltrating lymphocyte (TIL) therapy and engineered T-cell receptor (TCR) therapy [21].

d. Cancer Vaccines

Therapeutic cancer vaccines aim to stimulate the immune system to recognize and attack tumor-specific antigens [22]. HPV-associated HNSCC provides a unique opportunity for vaccine-based interventions, given the viral etiology [23]. Peptide-based, dendritic cell-based, and viral vector-based vaccines targeting HPV antigens are under clinical evaluation [24].

5. Emerging Therapies and Combination Strategies

Given the complexity of immune evasion mechanisms, combination therapies integrating ICIs with chemotherapy, radiation, or targeted therapies are being explored [25]. The rationale is to enhance antigen presentation, increase immune infiltration, and overcome resistance to monotherapies [26]. Preclinical and clinical studies suggest that multimodal approaches may provide synergistic benefits [27].

Ongoing Clinical Trials

Several ongoing clinical trials are investigating novel immunotherapeutic approaches in HNSCC. Trials exploring new checkpoint inhibitors, adoptive cell therapies, and combination regimens are underway. Data from these studies will provide insights into optimizing treatment strategies for HNSCC [28].

6. Challenges and Future Directions

Despite its potential, immunotherapy faces several challenges, including variable response rates, immune-related adverse events, and high treatment costs [29]. Biomarker-driven patient selection, optimization of combination strategies, and development of novel

immune targets are key areas for future research [30]. The integration of personalized medicine and advanced genomic profiling may further refine immunotherapeutic approaches [31].

7. Conclusion

Immunotherapy represents a paradigm shift in the treatment of HNSCC, offering durable responses in select patients [32]. While ICIs have gained approval and ACT and vaccine strategies are under investigation, further research is needed to enhance efficacy and broaden applicability [33]. Overcoming immune resistance and optimizing patient selection will be crucial in realizing the full potential of immunotherapy in HNSCC [34]

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