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The Treatment of Oral Squamous Cell Carcinoma with PD-1/PD-L1 Inhibitors

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Abstract:

Oral squamous cell carcinoma (OSCC) often presents insidiously and has a high proportion of late-stage diagnosis, with a five-year survival rate of only 50% to 60% for traditional combined treatment, indicating a poor overall prognosis. Immunotherapy has now become a hotspot in tumor research, yet there are still many research shortcomings in the immunotherapy of OSCC. This article reviews the application of PD-1/PD-L1 inhibitors in OSCC. The results show that this target is highly expressed in cancer tissues, promoting tumor progression and indicating a poor prognosis. These drugs can rebuild the body's anti-tumor immunity and effectively improve the survival outcomes of patients with advanced disease and platinum resistance. However, the efficacy of monotherapy is limited, with an effective rate of only 20% to 30%, accompanied by the risk of resistance and various adverse reactions. This study provides a theoretical reference for the clinical practice of immunotherapy for OSCC. Currently, the mechanisms of resistance and individualized treatment options remain unclear. In the future, it is necessary to precisely screen suitable candidates, continuously optimize combination treatment modes, and promote the standardized development of immunotherapy for OSCC.

Keywords: Oral squamous cell carcinoma; PD-1/PD-L1 inhibitor; immunotherapy.

1. Introduction

Oral squamous cell carcinoma (OSCC) is a type of malignant tumor originating from the stratified squamous epithelium of the oral mucosa, and it is also the most common type of malignant tumor in the oral and maxillofacial region, accounting for approximately 40% of squamous cell carcinomas in the head and neck (HNSCC). OSCC is the sixth most common malignant tumor globally, with its incidence rate continuing to rise in recent years [1]. According to the 2022 data from the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), there were 389,485 new cases of oral cancer globally, with Asia being the main high-incidence area. Due to the insidious onset of OSCC, atypical

early symptoms, and the lack of efficient screening methods, over 60% of patients are diagnosed at a late stage. Despite advancements in the comprehensive treatment of surgery combined with chemoradiotherapy, the five-year survival rate for patients remains at only 50% to 60% [2]. Therefore, improving the cure rate of OSCC and extending patient survival remain the research focus and challenge in the current field of oral cancer. In recent years, immunotherapy drugs represented by Programmed Death Receptor 1 (PD-1)/Programmed Death Ligand 1 (PD-L1) inhibitors have emerged as a significant new treatment option for patients with malignant tumors, owing to their superior clinical benefits and therapeutic potential. Research and application of these drugs have covered multiple tumor types, achieving remarkable progress in the treatment of malignant tumors such as lung cancer and gastric cancer. The survival of many advanced-stage patients has been extended, and their quality of life has also improved. Monotherapy has become the standard regimen for some patients, while combination therapy with chemotherapy, anti-angiogenic drugs, or other immune checkpoint inhibitors is emerging as an important direction for enhancing efficacy. Relevant clinical research continues to advance and breakthroughs are being made.

Despite the new breakthrough brought by PD-1/PD-L1 immunotherapy to OSCC, there are still key issues such as the lack of precise efficacy prediction markers, unclear mechanisms of immune resistance, no unified standard for combination therapy schemes, insufficient targeted research on high-grade OSCC in Asia, and an imperfect management system for immune-related adverse reactions. This study focuses on the aforementioned gaps and aims to explore existing combination therapy schemes for PD-1/PD-L1 inhibitors through analysis based on relevant molecular markers. The purpose of this paper is to sort out the immune regulatory network of OSCC, providing theoretical support for improving the efficacy of immunotherapy in clinical practice, optimizing comprehensive treatment strategies, and reducing ineffective medication and adverse reactions.Unlike previous reviews that focus primarily on clinical outcomes, this study deeply analyzes the immune regulatory network of OSCC. We specifically correlate molecular markers with mechanisms of immune resistance, providing a theoretical basis for overcoming drug resistance.This review also uniquely highlights the insufficient targeted research on high-grade OSCC in Asian populations and addresses the imperfect management system for immune-related adverse reactions, filling a gap in current literature regarding population-specific efficacy and safety protocols.

2. Pathophysiological Mechanism of OSCC

OSCC is a gradual process influenced by both genetic and environmental factors, exhibiting distinct stage characteristics. Long-term exposure to tobacco, alcohol, and betel nut in the environment, combined with HPV (Human papilloma virus, HPV) infection and chronic oral inflammation, along with individual genetic susceptibility, collectively initiates the carcinogenesis process [3,4]. In the early stages of the disease, oral mucosa may present with precancerous lesions such as leukoplakia and erythema, where cells proliferate abnormally but have not broken through the basement membrane. Some lesions can be reversed through intervention. If the progression continues, it may develop into carcinoma in situ, where cells lose their normal differentiation function but remain confined to the epithelial layer. Subsequently, cancer cells break through the basement membrane and infiltrate surrounding tissues, entering the invasive carcinoma stage, accompanied by increased angiogenesis to support tumor growth. Advanced OSCC mainly metastasizes to regional lymph nodes through lymphatic metastasis, and later may metastasize to distant organs such as the lungs and liver through hematogenous metastasis, ultimately forming a widespread metastatic late-stage tumor. Throughout this process, tumor cells gradually acquire the ability to invade and migrate, evading immune surveillance, ultimately affecting patient prognosis. Early detection and intervention are key to improving treatment outcomes.

In the initiation stage of OSCC carcinogenesis, environmental carcinogens, high-risk HPV infection, and chronic inflammatory stimuli form a synergistic effect. On the one hand, they induce mutations or abnormal expression of tumor suppressor genes and proto-oncogenes, leading to an imbalance between cell proliferation and apoptosis. On the other hand, they activate local immune responses, promoting high expression of tumor necrosis factor-α (TNF-α) in oral potentially malignant disorders (OPMD). The pro-inflammatory microenvironment mediated by TNF-α further amplifies gene damage, laying the foundation for OSCC carcinogenesis [5].

During the progression and invasion-metastasis stages of tumors, TNF-α emerges as a core driving factor. The mechanism involves neutrophils enhancing the invasive potential of OSCC cells through a TNF-α-dependent pathway [6]. TNF-α upregulates the expression of genes related to invasive pseudopodia (such as WASP and Arp2/3) and matrix metalloproteinases (MMPs), which collaboratively degrade the extracellular matrix (ECM), promote epithelial-mesenchymal transition (EMT), and angiogenesis mediated by vascular endothelial growth

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factor (VEGF). Meanwhile, the activation of EMT-related transcription factors (such as Snail and Twist) and the downregulation of E-cadherin facilitate the lymphatic and hematogenous metastasis of cancer cells to regional lymph nodes and distant organs

3. Molecular Mechanism of Action of PD-1/PD-L1 Inhibitors

The PD-1/PD-L1 pathway is an important negative regulatory pathway in the immune system, primarily exerting an immunosuppressive effect. Physiologically, it inhibits excessive activation of T cells, maintains immune tolerance, and prevents autoimmune reactions and tissue damage. In the tumor microenvironment, tumor cells highly express PD-L1, which binds to PD-1 on the surface of T cells, inhibiting T cell function and leading to tumor immune escape. This pathway is also a key target in tumor immunotherapy. Blocking PD-1/PD-L1 can restore the anti-tumor activity of T cells and exert tumoricidal effects. Furthermore, this pathway is involved in the regulation of chronic infections, autoimmune diseases, and organ transplant rejection, serving as an important molecular mechanism for maintaining immune homeostasis.

PD-1/PD-L1 inhibitors break the TME immunosuppressive network by competitively blocking the specific binding of PD-1 and PD-L1, achieving immune cell functional reprogramming and anti-tumor responses. During tumor progression, tumor cells and tumor-associated stromal cells highly express PD-L1, which binds to PD-1 on the surface of infiltrating T cells, recruiting SHP-1/2 tyrosine phosphatases, blocking the downstream PI3K/Akt and MAPK signaling pathways of TCR/CD28, leading to the functional exhaustion of $CD8^+$ effector T cells (decreased proliferation, cytotoxic activity, and secretion of IFN-γ and TNF-α), ultimately resulting in tumor immune escape [7]. PD-1/PD-L1 inhibitors can directly reverse this process by competitively binding to terminate immunosuppressive signals, restoring the proliferation and killing functions of $CD8^+$ exhausted T cells; simultaneously regulating the balance of $CD4^+$ T cell subsets, inhibiting the immunosuppressive effect of Treg cells, promoting Th1-type cell activation, enhancing the antigen-presenting ability of dendritic cells, improving the immunosuppressive phenotype of the TME, and activating innate immune cells such as NK cells through paracrine effects, synergistically enhancing tumor clearance efficiency. After the restoration of immune cell function, the body initiates a cascade reaction of "antigen recognition - immune activation - tumor killing" through the coordination of innate and adaptive immunity, inhibiting tumor proliferation, inducing apoptosis, and blocking angiogenesis and invasion and metastasis, ultimately achieving tumor shrinkage or disease stabilization.

4. Clinical Study on PD-1/PD-L1 Inhibitors in the Treatment of OSCC

PD-1/PD-L1 exhibits significantly abnormally high expression in OSCC tissues. Research has shown that the positive expression rates of PD-1 and PD-L1 in OSCC tissues are significantly higher than those in corresponding normal tissues adjacent to the cancer, with the high expression trend of PD-L1 being more prominent, and the difference in expression between the two is statistically significant ($P<0.05$) [8]. This expression feature suggests that the activation of the PD-1/PD-L1 pathway may be an important molecular event in the development of OSCC, and its specific high expression in tumor tissue provides a potential target for subsequent targeted therapy. The expression status of PD-1/PD-L1 is closely related to the key clinical pathological features of OSCC [9]. Among them, the positive expression rate of PD-1 was significantly higher in low to moderately differentiated OSCC tissues than in highly differentiated tissues ($P<0.05$), indicating that the expression level of PD-1 may increase with the degree of malignancy of tumor cells. The expression of PD-L1 is directly related to tumor metastasis and staging. In OSCC tissues with lymph node metastasis, the positive expression rate of PD-L1 is significantly higher than that in tissues without lymph node metastasis; The positive expression rate of PD-L1 in late stage (stage III-IV) OSCC patients was significantly higher than that in early stage (stage I-II) patients (all $P<0.05$). In addition, there was no significant correlation ($P>0.05$) between the expression of both and the patient's age, gender, location of onset, and tumor diameter [10], indicating that their expression mainly reflects the core pathological characteristics such as the malignancy and invasion and metastasis ability of the tumor.

The expression status of PD-1/PD-L1 is an important indicator for evaluating the prognosis of OSCC patients. The survival rate of OSCC patients with PD-1 negative expression was significantly higher than that of patients with PD-L1 positive expression, and the survival advantage of PD-L1 negative patients was also significant ($P<0.05$). This result is consistent with the fact that PD-L1, which is highly expressed in tumor tissue, can bind to PD-1 on the surface of immune cells, inhibit the anti-tumor immune function of T lymphocytes, and promote the immune escape mechanism of the PD-1/PD-L1 pathway that allows tumor cells to evade immune killing, leading to faster dis-

ease progression and shorter survival time in patients [11]. At the same time, combining the correlation characteristics between PD-1 and tumor differentiation degree, PD-L1 and metastasis and staging, it can be further inferred that OSCC patients with high expression of PD-1/PD-L1 often have higher malignancy and invasion risk, and their probability of poor prognosis is significantly increased.

Immunosuppression mediated by high expression of PD-1/PD-L1 is the core mechanism of OSCC progression, and traditional treatment for locally advanced patients has limited efficacy. PD-1 monoclonal antibodies have become a hot research topic during the perioperative period. As a highly selective PD-1 inhibitor, Trastuzumab can specifically block the PD-1/PD-L1 signaling pathway, reverse tumor immune escape, and rebuild the body's anti-tumor immune response. At the same time, domestic PD-1 inhibitors of Carilizumab have also been extensively explored in neoadjuvant therapy for locally advanced oral squamous cell carcinoma. A retrospective study involving 33 patients in the real world showed that neoadjuvant therapy using a combination of trastuzumab and chemotherapy resulted in an ORR of 66.7%, MPR of 54.5%, and pCR of 33.3%, and overall treatment safety was good without significant uncontrollable adverse reactions [12]. Multiple clinical studies have also confirmed that other domestic PD-1 inhibitors combined with chemotherapy can effectively reduce tumor burden and improve surgical resection rate. This result confirms that the combination of trastuzumab and chemotherapy can bring significant pathological relief benefits to locally advanced OSCC patients, providing reliable clinical evidence for perioperative immunotherapy.

5. Future Prospects

PD 1/PD L1 inhibitors have brought breakthrough progress to OSCC treatment by blocking immune checkpoints and restoring T cell anti-tumor activity. Compared to traditional radiotherapy and chemotherapy, it shows clear efficacy in locally advanced or metastatic OSCC, especially in platinum resistant patients, significantly prolonging survival and covering HPV related and unrelated subtypes of OSCC. This type of drug has better safety, with mild to moderate skin and gastrointestinal immune related events as the main adverse reactions. Combined with radiotherapy and anti-vascular drugs, it can further enhance tumor regression rate, significantly improve the quality of life and treatment tolerance of OSCC patients. However, the application of PD 1/PD L1 inhibitors in OSCC still has significant limitations. The single drug efficacy rate is only 20% to 30%, and most patients have primary drug resistance. The unique immunosuppressive microenvironment of oral cancer exacerbates the risk of secondary drug resistance. Among immune related adverse reactions, severe oral mucosal inflammation and rash have a higher incidence in OSCC patients, which increases the difficulty of management. In addition, the predictive value of biomarkers such as PD L1 expression and TMB in OSCC is limited, and drug accessibility and the physical condition of late-stage patients also limit their widespread application in OSCC populations.

The combination therapy of PD-1/PD-L1 inhibitors is a key direction to break through the treatment barriers of OSCC. In neoadjuvant therapy, its combination with platinum-based chemotherapy can significantly improve the main pathological remission rate and pathological complete remission rate of locally advanced OSCC, with better efficacy than monotherapy immunotherapy, and can improve long-term survival prognosis, laying the foundation for surgical degradation and functional preservation. Clinical studies on synchronous chemoradiotherapy combined with PD-1 inhibitors have shown significant survival benefits for operable patients, improved complete response rates for non-surgical patients, and lower incidence of serious adverse reactions, with controllable safety. In addition, the combination of inhibitors targeting key molecules and anti-angiogenic drugs can improve resistance mediated by OSCC angiogenesis mimicry, further enhancing therapeutic benefits.

OSCC comprehensive treatment will focus on precise screening, mechanism breakthroughs, and full process management in the future. At the biomarker level, the PD-L1 CPS score can guide the selection of monotherapy neoadjuvant therapy populations, and immune related gene expression subtypes can help predict the efficacy of combination radiotherapy and chemotherapy, providing a basis for individualized regimen development. In terms of treatment mode, the standardized surgical process after neoadjuvant therapy has gained consensus, and double standard evaluation is needed to avoid misjudgment of "false progress". Developing targeted combination therapies targeting vascular mimicry related regulatory pathways is expected to reverse drug resistance. Special populations can benefit cautiously under the guidance of multidisciplinary teams, and in the future, evidence-based research needs to be further expanded to promote the development of OSCC comprehensive treatment towards precision and long-term effectiveness.Future research needs to focus on optimizing combination therapy plans, and improving overall management.

6. Conclusion

PD-1/PD-L1 inhibitors provide a novel targeted therapy

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direction for OSCC. The main study of this article clarifies that OSCC is driven by genetic and environmental factors, progresses through multiple stages, and invades and metastasizes through immune escape. The PD-1/PD-L1 pathway is abnormally overexpressed in OSCC tissue, which is associated with tumor pathological characteristics and poor prognosis, and constitutes the core target of targeted therapy. These inhibitors demonstrate clear survival benefits and good safety in late stage and drug-resistant OSCC patients by blocking the pathway and reshaping the immune microenvironment. Combination therapy can further improve efficacy and has become a key component of comprehensive treatment. This result echoes the core demand of the traditional treatment dilemma of OSCC mentioned in the introduction, which not only deepens the understanding of the immunopathological mechanism of OSCC and adds efficient treatment options for clinical practice, but also provides important references for subsequent personalized treatment, biomarker mining, and combination therapy optimization. However, there are still limitations in this field, such as insufficient response to monotherapy, prominent drug resistance, and limited predictive efficacy of biomarkers.Despite the comprehensive analysis presented in this review, the current clinical application of PD-1/PD-L1 inhibitors in OSCC still lacks standardized biomarkers for precise patient selection, and the long-term efficacy and safety of combination therapies require further large-scale, high-quality prospective studies to validate.

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