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Advances in Oral Squamous Cell Carcinoma: Pathogenesis, Risk Factors

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Abstract:

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Among many types of Oral Cancer, Oral Squamous cell carcinoma(OSCC) is one of the most significant malignant tumors in the world. When more research is done into the molecular pathogenesis behind tumor initiation and progression, there is an opportunity to discover targeted therapies that are more effective for treatment. Moreover, in the study of tumor microenvironment,the interaction among cancer cells and surrounding stroma or immune cells, is also still not well understood. Understanding the interactions between molecules in the tumor microenvironment has important implications for the study of new therapeutic targets. The symptoms, pathogenesis and risk factor of OSCC as well as the existing therapeutic methods were studied in this paper. Because there are no obvious symptoms in the early stages of OSCC, it is important to know it for the treatment of OSCC. Risk factor also discussed the main causes of OSCC, which also can be contributed to the subsequent research. In this paper, common and popular therapies are listed. nanotechnology-based drug delivery is one of the most novel and effective therapies available today. This method offers the possibility of delivering chemotherapy or targeted drugs directly to OSCC. This reduces systemic side effects and provides precision. This technology has shown amazing effects in the clinical scope and is gradually being used in treatment.

Keywords: Oral Squamous Cell Carcinoma; tumor microenvironment; risk factors; targeted therapy

1. Introduction

Oral Cancer (OC), a common form of head and neck cancer, is caused by the proliferation of cells that are foreign to the upper and lower gums. These cancers are often mistaken for gingivitis. OCs are characterized by high morbidity and mortality and tend to spread to different parts of body including lung, liver, and bone. Despite advances in understanding the mutational features and dysregulated route of OC, patient survival has not improved significantly over the past decades. Squamous cell carcinoma, as

a type of OC, is the most common type of OC, counting for about 90% of all cases. Squamous cell carcinoma originates from squamous cells, which are flat, thin cells that cover the surfaces of the mouth, tongue, lips, and throat. Early detection and treatment are essential to improve the prognosis of patients with OSCC. Head and neck cancers account for 3-5% of all malignant tumors, of which 33% occur in the oral mucosa, which is one of the most common OCs. Oral squamous cell carcinoma (OSCC) mainly affects men at or over 50 years of age and is associated with long-term smoking and alcohol consumption. These risk factors that greatly increase the likelihood of developing cancer. Today, OSCC is growing to be one of the most common cancers, with an extremely high mortality rate. According to statistics, in 2020, 377,713 cases of OSCC were reported worldwide. To the data from Global Cancer Observatory (GCO), the incidence of OSCC is expected to increase by about 40% by 2040, along with an increase in mortality [1]. Various risk factors, including tobacco, alcohol, betel quid (BQ), and HPV, contributes to the growth of oral potentially malignant disease (OPMD), a lesion of the oral mucosa that has a very high risk of developing into OSCC, a complex and multifactorial cancerous process involving genetic alterations, epigenetic modifications, and a dysregulated tumor microenvironment. Various therapeutic techniques, such as chemotherapy, radiotherapy, immunotherapy, and nanomedicine, have been currently used to prevent or treat OSCC and OPMD, among which targeted agents, which have emerged as novel drugs in recent years, have brought more hope for the treatment of patients with advanced disease. Currently, various targeted therapeutic agents are undergoing various clinical trials in patients with OSCC.

2. Symptom

OSCC occurs in the oral mucosa and is a common malignant tumor of the head and neck. Early OSCC is characterized by a reddish-white or reddish mass with a slightly bumpy surface and well-defined borders. In the early stage of cancer, it is basically painless. As the disease progresses and reaches the advancement stage, ulceration occurs in the mouth, and the mass, with irregular edges, is hard to the touch and accompanied by discomfort. OSCC can appear anywhere, but the most likely location to occur are the tongue and the floor of the mouth, while other areas include the lips, the back of the molar region, the gums, the soft palate, and, less commonly, the back of the tongue and the hard palate. OSCC spreads primarily through the lymphatic flow to the ipsilateral lymph nodes in the neck, followed by invasion of the contralateral bar nodes and even bilateral lymph. The lungs, bones and liver are typical sites of OSCC metastasis. Early diagnosis plays an important role in the treatment of OSCC and minimizes the extent of surgery required. Statistically, patients who are detected at the first stage and treatment is initiated have a survival rate of 80-90%.

2.1 Pathogenesis

OSCC is usually experienced by multiple precursor stages that will cause morphological changes in the cells of the oral mucosa, leading to precancerous lesions such as erythema or leukoplakia.

2.1.2 Leukoplakia

Leukoplakia is a precursor to a confirmed diagnosis of OSCC. The global prevalence of leukoplakia is 4.11%, with the highest prevalence in Asian populations, at about 7.77% [2]. Malignant transformation of oral epithelial dysplasia is more likely to occur. Therefore, understanding the pathogenesis of leukoplakia can be of great help in stopping cancerous transformation. Both leukoplakia and OSCC arise from molecular abnormalities. The oncogenic potential of OPMD is increased by alterations in chromosomal regions of tumor suppressor genes or proto-oncogenes. According to a 1996 study of genetic variants in oral pre-cancerous lesions, chromosomal deletions on chromosomes 9p21 and 3p14 were found to increase the risk of OC in a sample [3]. Most of the genetic variants that lead to the emergence of head and neck cancer are mainly due to the activation of oncogenes and inactivation of tumor suppressor genes, resulting in excessive cell proliferation or death. Among the genetic variants observed are genetic variants in the tumor suppressor genes p16 and p53. P16 is a tumor suppressor protein that plays a crucial role in regulating the cell cycle. Gene inactivation of p16 will lead to defective cell growth, which will activate tumor growth. Meanwhile, TSG p53 plays an important role in cell cycle control and induction of apoptosis, while p53 possesses the role of maintaining genome stability, cell differentiation, and more. P53 dysregulation has a huge impact in leading to squamous cell carcinoma production. According to Cui et al, in an experiment to explore the expression of p53 in leukoplakia, p53 was found to be up-regulated in oral leukoplakia by using RT-PCR to detect p53 mRNA in patients with leukoplakia, and about 1.6% of the oral leukoplakia cases were p53-positive. In addition, OCs that developed from oral leukoplakia showed an increased p53-positive status, with a positivity rate of 3.4% [4].

2.1.2 Erythema

The presence of erythema is one of the symptoms of early OSCC. Erythema is characterized by smooth, granular, or

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nodular plaques that usually show a marked difference in edge separation from the normal oral mucosa. These red granular plaques with irregular surfaces may also stroll multiple irregular white or yellow spots, and these lesions are known as erythematous leukoplakia. Despite its low prevalence, erythema has a higher potential for malignant transformation relative to leukoplakia. Like leukoplakia, up to 46% of the erythema patients have p53, and the prevalence of p53 mutations observed in patients with erythema in this trial was significantly higher than that observed in leukoplakia, which is further suspected to be related to the high rate of malignant cancer conversion that erythema has [5].

2.2 Risk Factors

2.2.1 Smoking

Smoking as one of the most important contributors to OC, may increase the risk of developing the cancer up to 8.4% in smokers compared to non-smokers. Heavy carcinogens such as Nitroso compounds, polycyclic aromatic hydrocarbons and 4-(Methyltyramine)-1-(3-pyridyl)-1-butanone (NNK), which are contained in tobacco, are responsible for the malignant transformation of oral cells, and they can induce specific gene mutations, such as GT transitions in the genome [6]. When the oral mucosa is chronically exposed to carcinogens contained in tobacco, it leads to genetic changes in the epithelial cells, which randomly leads to genomic instability and ultimately to the development of cancerous lesions. Moreover, tobacco could activate the EGFR to promote the downstream pathway, stochastically through the activation of the cell cycle protein D1, which leads to stronger cell proliferation and increase the chance of genomic mutation. This uncertainty will further promote the development of oral cell carcinogenesis, resulting in irreversible damage.

2.2.2 Alcohol

According to the data provided by International Agency for Research on Cancer (IARC), alcohol is classified as a Class I carcinogen, and the carcinogenicity of ethanol stems from the major oxidative metabolite acetaldehyde mediated. ADH leads to the oxidation of ethanol to acetaldehyde. Acetaldehyde as an intermediate metabolite, has the ability to react with DNA, and the fusion of the two can lead to gene mutation or inhibition of DNA synthesis, which can further lead to cancer. Alcohol itself has a significant impact on the development of OCs, but when used in conjunction with tobacco, it can have an even more serious effect, greatly increasing the likelihood of cancer. In an experimental study conducted by Ko et al., it was found that the incidence of OC was 123% higher in those who smoked, drank and used betel compared to those who didn‘t [7]. Studies have shown that alcohol has the ability to cause cancer cells to cross cell membranes and by increasing the metabolic activity of the human liver, which also stimulates the differentiation of cancer cells. In addition, by altering the metabolic pattern of the oral epithelium, alcohol makes it easier for carcinogens still present in tobacco to affect the oral mucosa, leading to an increased likelihood of mutations and therefore making it more likely that cancer will develop in the oral cavity [8].

3. Treatment Options

3.1 Surgery

Treatment options for OC are further identified mainly based on the stage of the cancer. The choice of treatment should begin with a personalized plan tailored to the patient‘s requirements, formulated, and informed by consideration of the patient‘s actual financial situation as well as survival rate. In the early stages of the disease, most treatments include surgery or radiation therapy, however, when the cancer is in advanced stages, a variety of considerations are needed to maximize the survival rate and improve postoperative comfort. Surgery is generally one of the more common treatments and is the preferred first-line treatment for small, easily treatable squamous cell carcinomas of the oral cavity. Before undergoing surgery, patients should undergo comprehensive imaging to accurately determine the stage of the cancer. Currently, computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used to accurately determine the localized areas. OSCC is commonly found on the tongue, floor of the mouth, maxillary and mandibular gums, buccal mucosa, and hard palate. There are different surgical options for different areas. Adequate removal of tumor cells is the main goal of surgical treatment, and failure to adequately clear the cancer leads to an increased likelihood of local recurrence. Aesthetics are also a consideration. In resection of OSCC, it is acceptable to control the removal of marginal tissue to within 1 cm, and if this is exceeded it may result in compromised aesthetics or lead to an increased likelihood of dysfunction. Reconstructive surgery is necessary after removal of a large primary tumor for restoration of oral function and aesthetics. The most popular technique today is the use of free tissue grafts, starting from skin grafts to microvascular free flaps, and this technique is currently the most reliable reconstructive technique, with an overall success rate of 98% for reconstruction of surgical defective free flaps in oncology.

3.2 Nanoengineering Therapy

As a highly lethal cancer, even early stage of OSCC still has the possibility of recurrence, and the five-year overall survival rate for T1-T2 tumors is maintained at roughly 70-80%. For advanced stage patients, conventional treatment consists of surgery, sometime adjuvanted by chemotherapy. However, although surgery is the most used treatment, it always has a high recurrence rate and may cause irreversible dysfunction, which has a significant negative impact on the patient‘s swallowing, speaking, and chewing functions. Secondly, post-surgical treatment is usually supplemented using chemotherapeutic agents such as cis-dichlorodiammine platinum (CDDP). Cisplatin prevents the proliferation of DNA by cross-linking with the DNA within the strand, causing the cancer cells to wither away, however, this drug can also cause adverse effects on the patient‘s body, such as nausea, vomiting, acute nephrotoxicity, bone marrow suppression, and so on. So, while using the drug, the dosage needs to be reduced on a case-by-case basis. However, this situation can be improved and localized treatment of OCSCC only can effectively reduce or even eliminate the systemic toxicity associated with conventional cisplatin chemotherapy treatment. According to the study, by replacing the original cisplatin delivery method with a nanoparticle-based drug delivery system (DDS), the retention of the drug in the cancer cells can be effectively promoted, thereby facilitating an increase in cellular uptake. To eliminate the additional burden and malignant effects of common chemotherapeutic drugs on the body, Manijeh Goldberg et al. have nano-engineered a new therapeutic agent, PRV111 [9]. PRV111 is a self-adhesive cisplatin transmucosal system that delivers chitosan particles (CLPs) to various portions of the oral cavity, and the permeation enhancers (PEs) contained in the system are more effective in opening the mouth. Contained in the system opens cellular connections more efficiently, allowing for optimal CLP permeation and absorption within the tissues. When exposed to water, CLP swells and diffuses into the tumor cells; however, the swollen CLP is too large to penetrate the vascular system, so it is not exposed throughout the body in the same way as conventional cisplatin. Preclinical data demonstrated that PRV111 was safer and more effective than traditional cisplatin delivery regimens, and all animal specimens treated with PRV111 were free of tumor recurrence or tissue. In subsequent clinical testing, Goldberg et al. chose ten patients with confirmed (T1-T2, Nx, M0 [AJCC 7th Edition].) OCSCC and tumor size $\leq$ 4.0 cm. Eight of these patients experienced a 69% reduction in tumor volume within seven days of PRV111 treatment, with a response rate of over 87%. With a 69% reduction in tumor volume within seven days and a response rate of more than 87%, and with all patients with early stage OCSCC demonstrating good tolerability and no serious adverse events, this technology demonstrated significant success during the clinical period. This novel drug therapy was created in response to the toxicity as well as adverse effects associated with traditional systemic chemotherapeutic drugs. The absence of serious adverse effects and the lack of significant recurrence rates suggest that PRV111 will continue to be utilized as a strategy to “stop” the progression of cancer in subsequent therapeutic regimens.

3.3 EGFR Inhibitors

Epidermal Growth Factor Receptor (EGFR) is one of the most important targets for cancer therapy and has a major impact on cancer development and progression. Nowadays, EGFR inhibitors have been utilized in a variety of cancer therapies. In today‘s research, the EGFR pathway has been found to be associated with sensitivity to the conventional chemotherapeutic agent cisplatin, and EGFR inhibitors have been shown to be useful in the follow-up of patients who have failed cisplatin therapy. The ability of EGFR inhibitors to improve cisplatin sensitivity in OSCC cell lines was investigated in a study by Yukihiro Hiraishi, et al [10]. Hiraishi et al. evaluated the response to a specific EGFR tyrosine kinase inhibitor, AG1478, in combination with cisplatin in a cisplatin-resistant subclass of cultured OSCC cell lines and found that the combination was able to enhance inhibition of OSCC cells. was able to enhance the inhibition of OSCC cell growth, so the developmental potential of EGFR inhibitors in the treatment of OSCC was identified and awaits use in subsequent clinical studies.

4. Conclusion

This paper summarizes and analyzes the symptom, pathogenesis, main risk factors of OSCC and the current common or novel treatment methods. OCSS is most commonly found in the oral mucosa, and although this cancer has no obvious symptoms or pain in the early stages, OSCC has multiple prodromal stages that will cause changes in the shape of the mouth, and if a significant red or white mass appears in the mouth, OSCC is a possibility. Early diagnosis is critical to improving the curability of OSCC. The main risk factors that cause OSCC are alcohol and smoking. Bad living habits are more likely to lead to genomic mutations in oral cells, resulting in abnormal cell proliferation, which promotes the development of cancer cells. Class I carcinogens contained in tobacco and alcohol are more likely to cause mutations in genes or inhibit normal DNA synthesis, leading to abnormal cell activity.

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However, despite being one of the cancers with a higher mortality rate, OSCC is not without the possibility of cure. The more common treatment is surgical resection and the intervention of chemotherapy drugs, which are more common in early treatment. However, common chemotherapy drugs produce excess toxicity, which attacks the body's normal tissues. To solve this defect, nanotechnology based drug delivery has been proposed to provide more precise and detailed targeted therapy, while greatly reducing the side effects caused by chemotherapy drugs. Moreover, improving cisplatin sensitivity in OSCC cell lines with EGFR inhibitors is one of the key development goals. However, there are also unresolved issues in this paper. Tobacco and alcohol as foreign substances can cause changes in the genome, but whether OSCC is a genetic disease has not been discussed, and whether OSCC will be passed on to future generations is unknown.

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