

Progress of EGFR targeted therapy for oral cancer

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Abstract. Because of some uncertain factors such as eating habits and smoking, oral cancer has become one of the serious diseases of the oral and maxillofacial region. Especially in some Chinese cities where betel nut chewing is customary, the incidence of oral cancer has been high. Today, the main treatment methods are still traditional surgical excision, radiation and chemotherapy. However, with the development of medical technology, gene-targeted therapy has become the most important research object. Gene targeting technology is mainly targets the treatment of cancer organ cells, reducing the damage of traditional treatment methods on other areas without lesions. At present, the epidermal cytokine EGFR has been the most studied, and some research results have been put into clinical application. However, in terms of targeted therapy, the development of technology is still incomplete and immature. This article mainly discusses the pathogenic mechanism of EGFR in oral cancer, the synergistic effect of EGFR and other factors on the development of oral cancer, and the research results of EGFR-targeted therapy and combination therapy for oral cancer. The significance of this study is that based on these discussions, it provides reference opinions for treatment that can achieve a good prognosis for oral cancer patients and alleviate the pain of oral cancer patients, and evaluate the current development status of clinical application of EGFR targeted therapy for oral cancer. At present, the targeted therapy technology of oral cancer is still immature. In the future, the role of other factors in the development of oral cancer can be studied, and the influence of the combination of targeted therapy and other therapeutic methods on the treatment results of oral cancer can be studied.

Keywords: EGFR, oral cancer, target therapy.

1. Introduction

One of the most prevalent malignant tumors of the head and neck is oral cancer. It usually refers to carcinoma caused by squamous cell, which accounts for around 90% of all oral malignant tumors and develops in the oral mucosa [1]. At present, the exact cause of oral cancer has not been found. Current research shows that the main oral cancer risk factor is smoking. The interaction between alcohol and smoke can significantly increase the incidence of oral cancer. In addition, chewing betel nut is also one of the risk factors for oral cancer. In the human body, oral cancer is an epithelial invasive tumor with varying degrees of squamous differentiation and can occur in any part of the oral mucosa. Among people who often chew betel nuts and smoke, the buccal mucosa is a common site. One of the epidermal growth factor receptors, EGFR is found on the surface of many different types of cells, including keratinocytes, glial cells, fibroblasts, and mammalian epithelial cells. Studies have demonstrated that aberrant EGFR signaling can accelerate cellular growth, resulting in improper cell division and proliferation, and is a

key factor in the occurrence and growth of malignancies [2]. Many solid tumors have high or aberrant levels of EGFR expression, and EGFR is linked to the suppression of tumor cell growth, angiogenesis, invasion, metastasis, and death.

Traditional cancer treatment methods such as chemotherapy, radiotherapy and surgery, the 5-year survival rate is only about 50% ~ 60%, and about 1/3 of patients will relapse, and the swallowing, speech function and facial appearance of patients after surgical treatment are seriously affected, there are obvious and serious facial injuries, eating and language disorders, the main reason for affecting the survival rate is local recurrence and lymphatic metastasis [3, 4]. With the development of medical research, the main direction of study has turned to targeted cancer therapy. What targeted therapy means is targeting different targets of tumors at the organ tissue and molecular levels. Use different targeted therapy technologies to specifically treat tumors. EGFR is one of the main targets for targeted therapy of oral cancer, and a lot of research results have been applied in clinical practice [5].

But the targeted therapy also has some drawbacks, The main disadvantage of targeted therapy is that the number of patients who can really be suitable for targeted therapy and benefit from targeted therapy is relatively limited, because many targeted therapy drugs need to undergo gene detection before application, and only through gene detection to find suitable therapeutic targets can targeted therapy be carried out. For some targeted drugs that must be found to treat the target, if the gene test results do not find the target, the blind use of these targeted drugs is harmful, and cannot make the patient's condition get relief, but increases the incidence of adverse events. Another disadvantage of targeted therapy is that targeted therapy drugs still have a certain degree of adverse reactions. Despite the fact that most targeted therapy medications have fewer side effects than chemotherapy drugs, but they can frequently result in negative side effects different from those of chemotherapeutic medications. As an illustration, some targeted medications can result in severe diarrhea and rashes. Some can cause proteinuria, hypertension, hand-foot syndrome and other adverse reactions, need clinicians to give close attention and active treatment.

This article mainly summarizes the past research results on EGFR in oral cancer and the research on targeted therapy (EGFR) for oral cancer that has or has not been used clinically and proposes new directions that should be paid attention to in the future treatment of oral cancer.

2. Pathogenesis of EGFR in oral cancer

EGFR's full title is Epidermal Growth Factor Receptor, it is an Epithelial growth factor (EGF) receptor for cell proliferation and signaling. EGFR can induce epithelial cell proliferation, this receptor activation is very important for the immunity of epithelial tissue.

About one-third of human cancers have excessive or inappropriate expression of EGFR. The EGFR plays an important part in tumor angiogenesis, invasion, metastasis, and cell apoptosis inhibition. EGFR overexpression is present in glial cells, kidney cancer, lung cancer, prostate cancer, pancreatic cancer, breast cancer, and other tissues, and it plays a significant role in the development of malignant tumors[6-8]. Studies on glioblastoma have found that its gene amplification is primarily responsible for the highly expressed EGFR [9]. However, sometimes the abnormal regulation of EGFR expression level also exists in translation and post-translation. Intracellular signaling is significantly influenced by EGFR ligands. EGFR ligands activate EGFR in an autocrine manner to enhance cell proliferation, and their co-expression often predicts poor tumor prognosis.

Oral cancer is OSCC (Oral Squamous Cell Carcinoma), it is one of the most common malignant tumors in oral and maxillofacial region. At present, EGFR has been found to be overexpressed in up to 90% of OSCC cases [10]. In addition, EGFR gene mutations are also present in NSCLC (Non-small cell lung cancer). At present, the main research on EGFR is mainly for non-small cell lung cancer. Through EGFR gene mutation detection, it was found that its mutation was mainly in exon 18 to exon 21 of EGFR, and the most important type of mutation was the deletion of codon 746 to 750 in exon 19 and the point mutation of codon 858 in exon 21. These mutations can directly or indirectly lead to overexpression of EGFR, leading to malignant proliferation of epithelial cells. In addition, mutations in

these EGFR genes can also lead to increased resistance to chemotherapy or drug therapy. These factors together promote the development and deterioration of oral cancer [2].

2.1. EGFR promotes the stemness and progression of oral cancer by inhibiting SOX2

In a normal human body, the birth, growth, proliferation, differentiation, aging and death of each cell are strictly regulated and controlled by genes. In this way, the body can carry out orderly life activities. Of course, tumors are also the result of abnormalities in these genes. A tumor cell can be affected by different factors in the development of oral cancer. The transcription regulatory proteins of eukaryotic genes are also called transcription factors, and Sox2 is one of the transcription factors, which plays an important role in the early development of mammalian organs. Since transcription factors expressed by their coding genes into the nucleus can enhance or decrease gene expression, the regulation of transcription factor Sox2 in the development of oral cancer is also important in EGFR. Sox2 is a binding partner and substrate of EGFR, both of which are associated with poor prognosis of oral cancer. Studies have shown that EGFR signaling can enhance the dryness and progression of oral cancer by reducing the autophagy degradation of SOX2 and improving its stability [11]. Therefore, in the targeted therapy of oral cancer, human intervention in the process of EGFR intervention in Sox2 can be carried out through drugs or other means to control EGFR to reduce the enhancement effect of Sox2, thereby reducing the stability of Sox2 and promoting the autophagy degradation of Sox2 [11]. This has a very important role in promoting the good prognosis of oral cancer.

2.2. Effect of EGFR and CCND1 coordination on oral cancer

CCND1(Cyclin D1) is highly conserved to the cell cycle, and it plays an important role in the regulation of the mitotic time cycle. CCND1 can form complexes with CDK4 or CDK6 and act as their regulatory subunit, which drives the process of the cell mitosis cycle from the G1 to the S phase. Therefore, if the regulatory subunit formed by CCND1 and CDK4 or CDK6 is changed, that is, the CCND1 gene is mutated, amplified, or overexpressed, it will affect the cell cycle process. Moreover, the main function of CCND1 is to promote cell proliferation, so overexpression of this gene will lead to uncontrolled cell proliferation and malignancy. This phenomenon often occurs in the development of various tumors and may be the main cause of tumorigenesis. 2. Pathogenesis of EGFR in oral cancer and 2.1EGFR promotes the dryness and progression of oral cancer by inhibiting SOX2 can learn that EGFR plays an important role in the development of OSCC and can be developed in concert with other genes to promote OSCC dry-ness and development. The coordination of EGFR and CCND1 plays a very important role in the development of OSCC, and studies show that EGFR and CCND1 have an additive effect on the development of OSCC [12]. In this way, it can be proved that there is a probability of poor clinical effect after the targeted therapy of EGFR for oral cancer in some patients, and attention to the CCND1 gene is ignored. Therefore, in the targeted therapy of oral cancer, the corresponding treatment of these two genes can be carried out at the same time, so as to achieve better therapeutic effects.

3. Treatments of oral cancer

At present, the main treatment methods for oral cancer are still radical resection through surgery, or combined with radiotherapy and chemotherapy before or after surgery to achieve the expected therapeutic effect. The surgical treatment mainly includes radical resection, lymph node dissection and tissue defect repair. The main purpose of pre-operative radiotherapy is to reduce the risk of surgery, by reducing the number of tumor cells, reducing the size of the tumor to make the tumor easier to remove. Postoperative radiotherapy is mainly applied to the difficult or unresectable part of the operation for radical treatment of oral cancer.

There are also many other treatment methods for oral cancer, such as gene-targeted therapy, traditional Chinese medicine therapy, photodynamic therapy, etc., and studies have shown that psychological intervention after surgery can also effectively reduce patients' physical and psychological pain and improve the quality of life [13]. Moreover, studies have shown that traditional Chinese medicine treatment combined with chemotherapy can effectively reduce the immune dysfunction of

patients caused by chemotherapy, improve the therapeutic effect, alleviate the symptoms of oral cancer, and reduce the recurrence probability of oral cancer after treatment [14]. However, at present, some treatment methods are still not fully applied in clinical treatment or remain in the theoretical aspect.

3.1. Targeted therapy of oral squamous cell carcinoma

With the development of medical technology, surgical treatment, radiotherapy or chemotherapy can no longer meet the current demand for oral cancer treatment [15]. Although oral cancer is still mainly treated by traditional methods in clinical treatment, these traditional methods have some shortcomings that are difficult to solve, such as systemic toxicity, limited therapeutic effect, drug resistance and so on. Nowadays, the emergence of new technologies makes more and more people pay attention to the importance and feasibility of targeted therapy for oral cancer.

Targeted therapy is mainly through the identification of targets at the cellular and molecular level, these targets can be a protein molecule or a gene fragment, and the corresponding drug therapy or targeted radiotherapy and other treatment methods are carried out against these targets. These drugs or radioactive particles treat tumor cells without interfering with otherwise healthy tissue, reducing the limitations of traditional treatments. At present, the targeted therapy for oral cancer is mainly drug therapy. These drugs are EGFR-targeted drug therapy, VEGF receptor inhibitors, mTOR inhibitors, PD-1 targeted drugs, CDK inhibitors [16]. EGFR is a popular and most studied gene, among which two types of targeted drug therapy for EGFR in oral cancer have been applied in clinical treatment: 1. Tyrosine kinase inhibitors (TKI) such as gefitinib and afatinib. 2. Cetuximab and nituzumab are monoclonal antibodies that recognize the extracellular ligand-binding domain and interfere with receptor activation [16]. Some of these drugs have been found to have a certain relief effect on the pain of oral cancer research so for some patients with advanced oral cancer, these drugs can be used to perform labor pains to reduce the pain of patients with advanced cancer pain [17].

3.2. Clinical application of targeted therapy combined with Chemotherapy

Through the combination of radiotherapy, chemotherapy and surgery in traditional treatment methods, this idea can also be applied in the combination of targeted therapy and other treatments. This study can use the pain of oral cancer EGFR-targeted therapy drugs to cooperate with other treatments that will cause pain in patients, so as to achieve the effect of alleviating the pain of patients. In addition, by using the characteristics of targeted drugs, this study can carry out follow-up treatment for lesions that cannot be solved by traditional treatment or other treatment methods, so as to achieve a radical curative effect for oral cancer treatment [18]. In addition, in the treatment of oral cancer, some patients may take some analgesic or sedative drugs because of pain, but long-term use of these analgesic and sedative drugs will cause certain harm to the nervous system, digestive system, cardiovascular system and so on. The gene-targeted therapy drugs that have been tested in clinical trials can simultaneously treat oral cancer and labor pain, which can reduce the damage to the patient's body and reduce the poor prognosis.

4. Conclusion

By comparing and thinking about the existing treatment methods, it is not difficult to find that compared with the new treatment methods, the traditional treatment methods are more suitable for the current clinical treatment in terms of cost and popularity. Targeted therapy of EGFR for oral cancer is expensive and difficult to achieve in some underdeveloped areas, and people are more willing to trust traditional therapies than new ones. However, the new treatment methods, are more targeted, can effectively and purposefully solve the lesion, so as to achieve a very good therapeutic effect, and can make up for some shortcomings of traditional treatment methods. Compared with combined therapy, single therapy may not be effective in the treatment of oral cancer in some patients, but combined therapy can make up for the shortcomings of single therapy, so as to achieve the expected therapeutic effect. Overall, the advantages of targeted therapy for oral cancer (EGFR) outweigh the disadvantages at this stage, and its performance is satisfactory whether it is treated directly or in combination with other therapeutic methods. However, in future studies, as more and more people pay attention to the targeted therapy of

EGFR in oral cancer, it is possible to find its shortcomings. What researchers need to do is discover and find better treatments to save more lives.

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