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Advancements in Immunotherapy for Oral Cancer Research

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Abstract. Oral cancer is one of the common malignant tumors of the head and neck. The survival rate in the late stage is about 50%. At present, more and more immunotherapy is gradually used in the clinical treatment of oral cancer. Some relevant experiments on the efficacy of immunotherapy for the treatment of oral cancer are also actively carried out. However, at present, there is a lack of the latest experimental data on the review of immunotherapy for oral cancer, and the classification method is quite single. This paper divides oral cancer into three stages: prevention, early and late stages, and comprehensively evaluates and analyzes the application effects of immunotherapy at each stage. In particular, based on the KEYNOTE-048 trial data in February 2023, it elaborates on the therapeutic effect of Pembrolizumab in patients with advanced oral cancer. Although there are many types of immunotherapy, some are still only in the theoretical stage and have limited clinical data in oral cancer. At the same time, the treatment boundaries for different stages are still unclear, and clinical applications mainly depend on the patient's immune status and condition. This review aims to provide more valuable reference for further research.

Keywords: Oral cancer, TCR-T, TLR-DC-T, ICIs.

1. Introduction

All Oral cancer is a common malignancy of the head and neck. The patient's death is mainly due to the loss of control of the primary lesion. The average 5-year survival rate of each stage is between 50%~60% [1]. There are many predisposing factors for oral cancer, such as poor oral hygiene, long-term addiction to tobacco and alcohol, hypertension, and oral mucosal lesions [2]. Squamous cell carcinoma (SCC) accounts for more than 90% of all oral cancers. Other malignancies may arise from epithelium, connective tissue, small salivary glands, lymphoid tissue, and melanocytes, or metastases from distant tumors [3]

Immunotherapy has shown great potential in the treatment of tumors in recent years. There are a variety of treatments for oral cancer, such as radiotherapy, chemotherapy, surgery, immunotherapy, etc. After radiotherapy, patients will experience skin breakage, hair loss, gastrointestinal adverse reactions, etc. Radiation therapy to the head and neck is required in the treatment of oral cancer, which may cause tooth decay. In terms of chemotherapy, mild symptoms include nausea and vomiting, hair loss, abdominal pain and diarrhea; In severe cases, it can cause toxicity to organs such as the liver, heart, and bladder. However, surgical therapy is less practical, and although it is effective when used in the early stage, about 60% of patients with oral cancer are found to be at an advanced stage, so in patients with advanced oral cancer, surgical treatment alone is not effective [4].

In recent years, a variety of immunotherapies have emerged, such as tumor vaccines, adoptive immunotherapy, cytokine therapy, etc. However, immunotherapy is developing rapidly, and there is a lack of systematic review of the current technologies of immunotherapy. The purpose of this article is to review the different effects of different types of immunotherapies on the treatment of oral cancer, and to comprehensively analyze the advantages and disadvantages of different therapies, so as to provide a comprehensive and valuable strategy for the immunotherapy of oral cancer.

2. Prevention of Oral Cancer

2.1. Prophylactic Vaccines:

T HPV vaccine is a vaccine used to prevent diseases caused by human papillomavirus, such as cervical cancer and genital warts. The vaccine is expressed using recombinant DNA technology, which induces the body to produce antibodies to eliminate the HPV virus before it infects normal cells.

There are currently three types of HPV vaccines: bivalent, quadrivalent, and nine-valent. The bivalent vaccine is primarily aimed at preventing cervical cancer caused by HPV16 and HPV18, which is effective in preventing cervical cancer. The quadrivalent HPV vaccine offers more protection against HPV, including types 16 and 18, and also adds types 11 and 6 (these are the main virus types that cause genital warts).

Current oral cancer primarily relies on the nine-valent HPV vaccine. A study assessing the risk of cancer caused by high-risk HPV viral infections shows that patients already infected with HPV-16 have a risk 5.95 times higher of developing oral squamous cell carcinoma compared to non-infected individuals. The total HPV infection rate in oral cancer patients in China is slightly above 50% (52%), with an HPV-16 infection rate of 42%. The HPV-18 type has a relatively lower infection rate of 22% [5]. The nine-valent HPV vaccine thus plays a significant role in preventing oral cancer. In terms of treatment efficacy, the HPV vaccine has been effective for up to 6 years, with 82.4% effectiveness against HPV 16/18, 75.3% against HPV 31/45, and 69.9% against HPV 31/33/45. The relative reduction rate for HPV 16/18 is 82.4% [6]. Compared to adults who have not been vaccinated, adults who have been vaccinated have a lower prevalence of oral HPV types 6, 11, 16, and 18 [7].

However, there is still a lot of controversy about the correlation between oral cancer and HPV virus. Among them, two scholars, Christian U Hübbers and Baki Akgü, clearly pointed out in the article that although there is a high correlation between oropharyngeal squamous cell carcinoma and HPV virus, there is no great correlation with oral squamous cell carcinoma, and even contradictory studies have appeared. Therefore, further research is needed on the association between high-risk HPV virus and OSCC [8].

2.2. Lifestyle Habits

Physical activities such as cycling or ball games are protective factors against oral cancer. On the other hand, in the risk factors for oral cancer, hypertension and waist-to-hip ratio, which reflects obesity, showed significant statistical differences in the analysis [2]. Therefore, it is important to prevent oral cancer from a lifestyle perspective.

The harm of tobacco and betel nut to oral health is tremendous.Although there may be some regional differences depending on the processing and consumption methods, the International Agency for Research on Cancer (IARC) also points out that there is sufficient evidence that betel nut can cause cancer. Another risk factor is nicotine, a key component of cigarettes. Vascular endothelial growth factor (VEGF) plays a significant role in the formation of tumor blood vessels, and VECF can be successfully induced and secreted when nicotine is present in non-neuronal tissues [9]. There is also evidence that exposure to nicotine can cause DNA damage within cells, activate intracellular signaling pathways, induce cytotoxicity, and thus promote the occurrence and development of oral cancer.

Therefore, by quitting smoking, drinking, and betel nut, and adopting a healthier lifestyle, it plays an indispensable role in preventing oral cancer.Literature References

References are cited in the text just by square brackets [1]. (If square brackets are not available, slashes may be used instead, e.g., /2/.) Two or more references at a time may be put in one set of brackets [3, 4]. The references are to be numbered in the order in which they are cited in the text and are to be listed at the end of the contribution under a heading *References*, see our example below.

3. Early Treatment of Oral Cancer

Immunotherapy is a new tumor treatment strategy, which can effectively enhance the specific response to tumors through the application of biological techniques and immunological methods. The 2013 scientific journal evaluated tumor immunotherapy as the most important scientific breakthrough. In 2020, the Nobel Prize in Chemistry was awarded to French microbiologist Emanuelle Charpentier and American biologist Jennifer Doudna in recognition of their "development of genome editing methods." Immunotherapy includes multiple types, such as adoptive immunotherapy, cytokine therapy, tumor vaccines, gene therapy, etc.

The most important purpose of early treatment of oral cancer is to completely eliminate the tumor and prevent recurrence. At this time, the role of immunotherapy is to reduce the volume of tumors and kill residual cancer cells after surgery, reducing the recurrence rate. In view of the early treatment methods, surgery is generally the main method, and immunotherapy appears as an auxiliary method.

Today, the immunotherapy used in the early days is PD-1 inhibitors. PD-1 (programmed death receptor 1) is a protein expressed on the surface of T cells, and when combined with PD-L1 (programmed death ligand 1) on tumor cells, it can inhibit T cell activity, thereby reducing the efficiency of tumor cells being killed by T cells.

And Nivolumab (PD-1 inhibitor), by blocking the combination of the two, removes the restriction on T cells, reactivating the T cells to exert a clearance effect on tumor cells.

Professor Guo Ye from the East Hospital of Tongji University pointed out in an interview that when patients undergo immunotherapy without surgery, radiotherapy and chemotherapy, immunotherapy PD-1 can exert the greatest efficacy because of the good immune status. Radiotherapy and chemotherapy can kill cancer cells and control tumors, but they also destroy the body's own immune cells. Immunotherapy is less effective when used in the setting of poor immune status.

Navuliyumab is also often used clinically to treat precancerous lesions of oral cancer (high-risk oral precancerous lesions). Clinical data show that among the 33 patients treated with navulizumab, a total of 9 patients developed OSCC during the trial, accounting for about 27% of the proportion. At the same time, seven patients suffered an adverse immune response. The side effects of Navulyumab are mainly clinically manifested as fatigue, oral pain, and gastrointestinal adverse reactions [10].

4. Advanced Treatment of Oral Cancer

The goal of advanced treatment of oral cancer is to control tumor growth, improve the quality of life of patients, and prolong survival time. At this point, immunotherapy works by using more direct immune cells to enhance immune stimulation. In advanced stages, it is not advisable to carry out any one treatment alone, and comprehensive treatment is the best choice for patients. Recurrent and metastatic are the difficulties and priorities of advanced oral cancer, but immunotherapy has brought us new hope and opportunities.

4.1. Immune Checkpoint Inhibitors (ICIs)

Currently, there are many studies that have shown promise for ICIs in treating oral squamous cell carcinoma (OSCC).

For example, anti-PD-1/PD-L1 drugs promote immune responses against tumors by blocking inhibitory signals at immune checkpoints. (Pembrolizumab and Nivolumab) are applicable to various stages of oral cancer.

Recurrent and metastatic oral cancer is properly resolved in aggregate remedy with pembrolizumab. In KEYNOTE-048, pembrolizumab in mixture with chemotherapy appreciably progressed standard survival as compared with cetuximab inside the typical populace (thirteen months VS 10.7 months). In terms of protection, the mortality rate of patients in the pembrolizumab alone group was eight% and that within the cetuximab mixed chemotherapy organization was 10%, compared with the safety

development within the pembrolizumab institution; amongst grade three or extra all-purpose destructive activities, the occurrence prices of pembrolizumab on my own organization, pembrolizumab combined chemotherapy group and cetuximab blended chemotherapy organization have been 55%, eighty five%, and 88%, respectively, without a sizeable difference. as compared with chemotherapy, this technique has a longer period and a better protection [11]. Taken collectively, pembrolizumab in combination with platinums and 5-fluorouracil and pembrolizumab by myself are appropriate first-line redress for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) [12].

Although pembrolizumab is effective, its toxic side effects should not be underestimated. Fatigue, mouth pain, and diarrhea are relatively common side effects. The mortality rate of immune myocarditis caused by PD1 therapy is as high as 46%, and there is no effective intervention, so the use of immune checkpoint drugs should be cautious to avoid possible serious complications [13].

4.2. TLR-DC-T Therapy

Toll-like receptors (tlrs) are an important pattern reputation receptor which can be often expressed in immune cells and numerous tumor cells. tlr7/8 is a Toll-like receptor inside the endosome, which participates in tumor immune monitoring and can understand the nucleic acids of microorganism. despite the fact that the mechanism of action of tlr7/eight in tumor immunotherapy is not but clean, tlrs on t cells are concerned inside the regulation of t cell feature and act as co-stimulating molecules to activate t cellular immunity. tlr agonist can prompt t cell-mediated antitumor response thru innate and adaptive immune responses to enhance tumor remedy [14]. In current years, new tablets with one-of-a-kind scaffolds of tlr7 or tlr8 agonist were evolved. these agonist retailers can set off the production of positive cytokines and chemokines, can be used within the treatment of certain diseases, and may be used as proper adjuvants for vaccines.

This remedy also indicates brilliant capacity within the treatment of oral cancer. In a look at of patients with superior head and neck squamous mobile carcinoma (HNSCC), improved TLR7 tiers have been located in forty two.nine% of sufferers, and TLR ligands were proven to have antitumor outcomes in one of a kind sorts of most cancers [14].

4.3. TCR-T Therapy

TCR-T therapy is quite just like automobile-T remedy, each concerning the ex vivo cultivation of T cells and their next reinfusion into the frame as an adoptive immunotherapy. while car-T remedy has proven tremendous efficacy against hematological tumors, it's miles much less effective against strong tumors. TCR-T therapy has the potential to conquer the limitations of vehicle-T therapy in treating stable tumors. It makes use of an allosteric dimer composed of alpha and beta peptide chains to apprehend peptide fragments offered at the surface of cells through the essential histocompatibility complex (MHC), and through genetic change, it complements the affinity of T cells with weaker recognition of tumor antigens [13].

TCR-T remedy has shown wonderful capacity within the treatment of non-small mobile carcinoma. among them, ADP-A2M4CD8 is an engineering T cell remedy. The medical and translational information of the segment 1 SURPASS scientific trial (NCT04044859) of ESMO ADP-A2M4CD8 show that as of March 9, 2023, 51 patients with cancer, non-small cell lung cancer, ovarian most cancers, gastroesophageal cancer, head and neck most cancers or UROTHELIAL most cancers have acquired 1.02-nine.95 x10^nine ADP-A2M4CD8 T cell transplantation.

The median (range) of previous redress was once three (1-8), with an H score for MAGE-A4 expression of 250 (90-three hundred). The four maximum commonplace damaging reactions related to T-cell therapy had been: cytokine launch syndrome (CRS) in 38 instances (74. five%), ≥3 grade in 7 instances (thirteen.7%), neutropenia in 27.5%, fever and fatigue in 21.6% every. CRS is achievable and can be treated with tocilizumab and corticosteroids as wanted.

The full performance of RECIST v1.1 in 45 monotherapy sufferers was 35.6% (2 cases had been in entire remission [CR] and 14 instances have been in partial remission [PR]). The median effective time was once 20. seventy-nine weeks (ninety-five% CI: 11.6, 30.9). There were thirteen clinical responses in a single treatment organization of 26 sufferers with ovarian cancer, urothelial most cancers and head and neck most cancers, with a powerful fee of 50%. some of the patients assigned to the nivolumab combination organization (n=6), there was 1 case of PR, 3 instances have been solid, and 2 cases couldn't be evaluated (2 sufferers did now not receive nivolumab treatment, and there was no publish-baseline RECIST evaluation).

From this, we will see that TCR-T has exceptional potential inside the remedy of HNSCC and will definitely play a great role in the future

5. Conclusion

Nowadays, there are many reviews of immunotherapy related to oral cancer. This article classifies oral cancer according to prevention, early stage, and advanced stage. Traditional reviews simply list different immunotherapies according to different mechanisms of action. Compared with the traditional classification method, the advantage of the method adopted in this paper is that the selection of clinical oral cancer immunotherapy is more methodical and more targeted for the treatment of patients. Based on the experimental data of the KEYNOTE-048 trial in February 2023, this article describes the therapeutic effect of pembrolizumab in patients with advanced oral cancer. At the same time, it also contains many documents from 22 years later, which is more time-sensitive.

Although there are many types of immunotherapies, there are still some that are currently in the theoretical stage, and there is a lack of clinical data on some specific applications and oral cancer. Secondly, the boundaries of medication for different stages of oral cancer are not clear. Because immunotherapy kills and controls cancer cells by regulating and stimulating the immune system, the clinical application is mainly based on the patient's immune status, specific condition, tumor type, and treatment history.

On the other hand, immunotherapy still has great limitations in the clinical treatment of oral cancer. The classification purpose of this article is mainly to provide data and strategic support for different stages of immunosuppression, and it is for reference only. Finally, because the mechanism of action of immunotherapy is not the main purpose of this article, the mechanism of action of individual immunotherapy has not been explained in detail.

In summary, immunotherapy is increasingly playing an irreplaceable role in the treatment of oral cancer.

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