International Journal of Clinical Case Reports 2024, Vol.14, No.3, 132-143
http://medscipublisher.com/index.php/ijccr

Research Report Open Access

Peptide-Based Vaccines for Oral Cancer: Mechanisms of Action and Clinical Outcomes

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International Journal of Clinical Case Reports 2024, Vol.14, No.3 doi: 10.5376/ijccr.2024.14.0015
Received: 23 Apr., 2024
Accepted: 28 May, 2024
Published: 07 Jun., 2024

Preferred citation for this article:
Xu W., and Li J.H., 2024, Peptide-based vaccines for oral cancer: mechanisms of action and clinical outcomes, International Journal of Clinical Case Reports, 14(3): 132-143 (doi: 10.5376/ijccr.2024.14.0015)

Abstract Peptide-based vaccines have emerged as a promising approach for the treatment of oral cancer, leveraging the ability to elicit robust anti-tumor immune responses. These vaccines primarily target tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) to stimulate CD8+cytotoxic T cells and CD4+helper T cells, thereby enhancing the body's immune response against cancer cells. Despite their potential, the clinical efficacy of peptide-based vaccines has been limited due to factors such as insufficient immune cell infiltration and the immunosuppressive tumor microenvironment. Recent advancements have focused on optimizing peptide sequences, incorporating potent adjuvants, and employing combinatorial therapies with immune checkpoint inhibitors to improve clinical outcomes. Personalized peptide vaccines, designed based on individual tumor neoantigens, represent a significant advancement, offering tailored immunotherapy with enhanced specificity and efficacy. This study discusses the mechanisms of action, clinical outcomes, and future prospects of peptide-based vaccines in the context of oral cancer, highlighting the importance of continued research and development to overcome current challenges and improve therapeutic efficacy.

Keywords Peptide-based vaccines; Oral cancer; Tumor-associated antigens (TAAs); Immune checkpoint inhibitors; Neoantigen-based vaccines

1 Introduction

Oral cancer, a subset of head and neck cancers, is a significant global health concern due to its high morbidity and mortality rates. It primarily affects the squamous cells lining the oral cavity and oropharynx. Risk factors include tobacco use, alcohol consumption, and human papillomavirus (HPV) infection. Despite advances in surgical techniques, radiation therapy, and chemotherapy, the prognosis for oral cancer patients remains poor, with a five-year survival rate of approximately 50% (Parmiani et al., 2014; Liu et al., 2021). This underscores the urgent need for novel therapeutic strategies to improve patient outcomes.

Peptide-based vaccines have emerged as a promising approach in cancer immunotherapy. These vaccines utilize short sequences of amino acids (peptides) that mimic tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) to elicit a targeted immune response(Naciute et al., 2020). The primary mechanism involves the activation of CD8+cytotoxic T lymphocytes and CD4+helper T cells, which recognize and destroy cancer cells presenting these antigens (Khong and Overwijk, 2016; Tardón et al., 2019; Liu et al., 2021). Recent advancements have focused on optimizing peptide sequences, incorporating adjuvants, and utilizing delivery systems to enhance the immunogenicity and clinical efficacy of these vaccines (Yang et al., 2015; Zamani et al., 2020; Abd-Aziz and Poh, 2020). Despite some challenges, such as limited potency and the immunosuppressive tumor microenvironment, peptide-based vaccines have shown potential in preclinical and clinical settings (He et al., 2018; Jiang et al., 2022).

This study investigates the mechanisms of action and clinical outcomes of peptide-based vaccines specifically targeting oral cancer. By reviewing existing literature and analyzing clinical trial data, the research aims to comprehensively understand how to optimize these vaccines to enhance therapeutic efficacy. The study covers the selection of appropriate peptide antigens, the role of adjuvants and delivery systems, and the potential of

combination therapies to overcome current limitations. This research contributes to the development of more effective peptide-based vaccines for oral cancer, offering new hope for patients battling this devastating disease.

2 Research Progress in Oral Cancer

2.1 Advances in understanding oral cancer biology

Oral cancer, primarily squamous cell carcinoma, is a significant global health issue. Recent research has elucidated various molecular mechanisms underlying its pathogenesis. Tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) have been identified as key players in the development and progression of oral cancer. These antigens are recognized by the immune system, which can be harnessed for therapeutic purposes (Hirayama and Nishimura, 2016; Abd-Aziz and Poh, 2020). Additionally, the role of genetic mutations and epigenetic modifications in oral cancer has been extensively studied, providing insights into potential targets for novel therapies (Hirayama and Nishimura, 2016; Liu et al., 2021).

2.2 Diagnostic innovations for oral cancer

Advancements in diagnostic technologies have significantly improved the early detection and management of oral cancer. Techniques such as liquid biopsy, which involves the analysis of circulating tumor DNA (ctDNA) and other biomarkers in bodily fluids, have shown promise in non-invasive cancer detection (Malonis et al., 2019). Imaging technologies, including advanced MRI and PET scans, have enhanced the accuracy of tumor localization and staging (Liu et al., 2021). Moreover, the development of molecular diagnostic tools, such as next-generation sequencing (NGS), has enabled the identification of specific genetic alterations associated with oral cancer, facilitating personalized treatment approaches (Hirayama and Nishimura, 2016; Tardón et al., 2019; Hamley, 2022).

2.3 Current therapeutic approaches for oral cancer

The treatment landscape for oral cancer includes surgery, radiation therapy, and chemotherapy. However, these conventional therapies often come with significant side effects and limited efficacy in advanced stages. Immunotherapy has emerged as a promising alternative, with immune checkpoint inhibitors showing clinical benefits in some patients (Hirayama and Nishimura, 2016; Tardón et al., 2019). Additionally, targeted therapies that inhibit specific molecular pathways involved in tumor growth and metastasis are being explored. Combination therapies, which integrate traditional treatments with novel agents, are also under investigation to enhance therapeutic outcomes (Bezu et al., 2018; Liu et al., 2021).

2.4 Research on vaccine development for oral cancer

Peptide-based vaccines represent a novel and promising approach in the fight against oral cancer. These vaccines are designed to elicit robust immune responses by targeting TAAs or TSAs specific to oral cancer cells (Abd-Aziz and Poh, 2020; Hirayama and Nishimura, 2016). The development of personalized peptide-based vaccines, which are tailored to the unique antigenic profile of an individual's tumor, has shown potential in enhancing antitumor immunity (Figure 1) (Hirayama and Nishimura, 2016; Bezu et al., 2018). Clinical trials have demonstrated that peptide-based vaccines can induce specific T-cell responses, although their efficacy varies among patients . To improve the clinical success of these vaccines, researchers are investigating the use of adjuvants and delivery systems that enhance immune activation and target antigen presentation (Malonis et al., 2019; Zamani et al., 2020). Combination therapies that integrate peptide-based vaccines with immune checkpoint inhibitors or other immunomodulatory agents are also being explored to overcome the immunosuppressive tumor microenvironment and improve therapeutic outcomes (Hirayama and Nishimura, 2016; Bezu et al., 2018; Malonis et al., 2019).

Significant progress has been made in understanding the biology of oral cancer, developing advanced diagnostic tools, and exploring innovative therapeutic approaches. Peptide-based vaccines hold substantial promise as a targeted and personalized treatment strategy, with ongoing research focused on optimizing their efficacy and clinical application (Hirayama and Nishimura, 2016; Bezu et al., 2018; Tardón et al., 2019; Abd-Aziz and Poh, 2020; Liu et al., 2021).

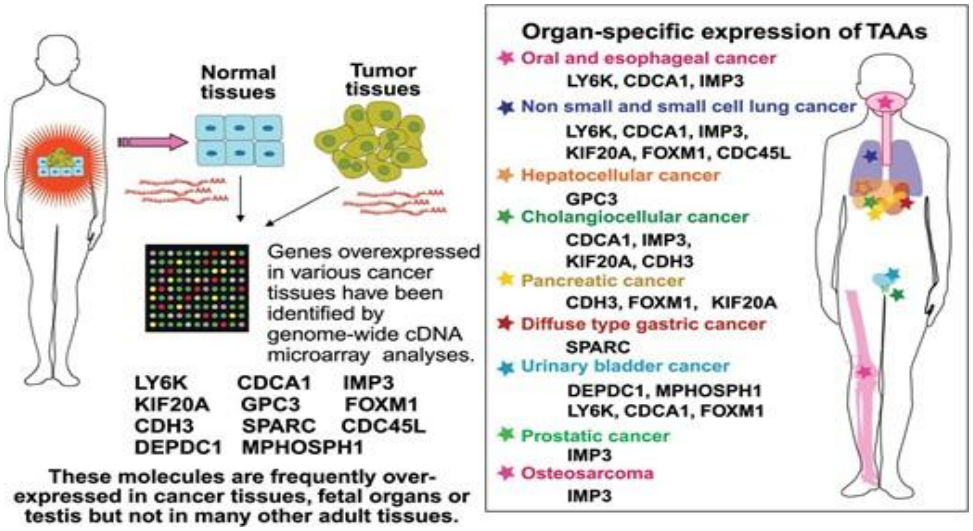

Figure 1 Organ-specific Expression of Tumor-associated Antigens (TAAs) in Different Cancers (Adopted from Hirayama and Nishimura, 2016)

Image caption: The gene were investigated using a genome-wide cDNA microarray analysis. These expression profiles of both various tumor tissues and normal tissues data enable us to identify novel TAAs frequently over-expressed in various malignant tumors and have the characteristics of CTAs or OFAs as ideal targets for cancer immunotherapy (Adopted from Hirayama and Nishimura, 2016)

3 Mechanisms of Action of Peptide-Based Vaccines in Oral Cancer

3.1 Immunological basis

Peptide-based vaccines for oral cancer are designed to stimulate the immune system to recognize and attack cancer cells. These vaccines typically target tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) that are presented on the surface of cancer cells. The immune response is primarily mediated by T cells, particularly CD8+ cytotoxic T lymphocytes (CTLs) and CD4+helper T cells. Upon vaccination, peptides are processed and presented by antigen-presenting cells (APCs) on major histocompatibility complex (MHC) molecules. This presentation activates T cells, which then proliferate and differentiate into effector cells capable of targeting and killing cancer cells expressing the same antigens (Bezu et al., 2018;Tardón et al., 2019; Buonaguro and Tagliamonte, 2023).

The immunological basis of peptide vaccines also involves the use of adjuvants to enhance the immune response. Adjuvants are substances that boost the body's immune response to the vaccine. They can help to increase the immunogenicity of the peptides, ensuring a more robust and sustained immune response. Common adjuvants include aluminum salts, oil emulsions, and newer formulations such as liposomes and nanoparticles (He et al., 2018; Zamani et al., 2020).

3.2 Peptide design and selection

The design and selection of peptides for cancer vaccines are critical for their efficacy. Peptides are chosen based on their ability to bind to MHC molecules and be recognized by T cells (Lazoura et al., 2005). The selection process involves identifying epitopes from TAAs or TSAs that are highly expressed in oral cancer cells. These epitopes must be capable of eliciting a strong immune response without causing autoimmunity (Stephens et al., 2021; Abd-Aziz and Poh, 2022).

Recent advancements in peptide design include the use of synthetic long peptides (SLPs) and multi-epitope peptides. SLPs contain multiple epitopes that can be processed by APCs to generate a broader immune response. Multi-epitope peptides combine several epitopes from different antigens, increasing the likelihood of generating a robust and diverse T cell response. Personalized peptide vaccines, which are tailored to the unique antigenic profile of an individual's tumor, are also being explored to enhance the specificity and efficacy of the immune response (Bezu et al., 2018; Liu et al., 2021).

3.3 Vaccine delivery systems

Effective delivery systems are essential for the success of peptide-based vaccines. Traditional delivery methods, such as subcutaneous or intramuscular injections, often require the use of adjuvants to enhance the immune response. However, newer delivery systems are being developed to improve the stability, bioavailability, and immunogenicity of peptide vaccines (He et al., 2018; Zamani et al., 2020).

Nanoparticles, liposomes, and other nanomaterials are being investigated as delivery vehicles for peptide vaccines. These systems can protect peptides from degradation, facilitate their uptake by APCs, and provide sustained release of the antigen. For example, liposomal formulations containing long multi-epitope peptides have shown promise in preclinical models by inducing strong CD4+ and CD8+ T cell responses and reducing tumor growth6. Additionally, the use of delivery systems that target specific tissues or cells can enhance the precision and effectiveness of the vaccine (He et al., 2018; Stephens et al., 2021).

3.4 Interaction with tumor microenvironment

The tumor microenvironment (TME) plays a significant role in the efficacy of peptide-based vaccines. The TME is often immunosuppressive, with various factors such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and immunosuppressive cytokines that inhibit the immune response. Overcoming this immunosuppressive environment is crucial for the success of cancer vaccines (Tardón et al., 2019; Buonaguro and Tagliamonte, 2023).

Strategies to modulate the TME include the use of combination therapies that pair peptide vaccines with immune checkpoint inhibitors, such as anti-PD-1 or anti-CTLA-4 antibodies. These inhibitors can block the pathways that suppress T cell activity, thereby enhancing the immune response to the vaccine. Additionally, the use of adjuvants that activate innate immune responses can help to reprogram the TME to be more supportive of anti-tumor immunity (Parmiani et al., 2014; Bezu et al., 2018).

Peptide-based vaccines for oral cancer leverage the body's immune system to target and destroy cancer cells. The success of these vaccines depends on the careful design and selection of peptides, effective delivery systems, and strategies to overcome the immunosuppressive tumor microenvironment. Ongoing research and clinical trials continue to refine these approaches, with the goal of improving the clinical outcomes for patients with oral cancer.

4 Preclinical Studies on Peptide-Based Vaccines for Oral Cancer

4.1 In vitro studies

In vitro studies are crucial for understanding the fundamental mechanisms of peptide-based vaccines and their potential efficacy against oral cancer. These studies typically involve the use of cancer cell lines to evaluate the immunogenicity and cytotoxic effects of peptide vaccines. For instance, peptide vaccines designed to target tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) have shown promise in eliciting strong immune responses. The peptides are often modified to enhance their immunogenicity, which can lead to a more robust activation of T cells (Parmiani et al., 2014; Liu et al., 2021; Abd-Aziz and Poh, 2022).

One significant advantage of peptide-based vaccines is their ability to be synthesized easily and their minimal side effects when administered in vivo. This has been demonstrated in various cancer types, including oral cancer, where peptides derived from TAAs can successfully elicit CD8+and CD4+T cell-specific responses (Brinkman et al., 2004; Peres et al., 2015; Khong and Overwijk, 2016). The use of adjuvants in these vaccines is also critical, as they can significantly enhance the immune response by promoting the activation and maturation of dendritic cells, which are essential for T cell activation (Khong and Overwijk, 2016; Abd-Aziz and Poh, 2022).

4.2 Animal models

Animal models play a pivotal role in preclinical studies by providing a more comprehensive understanding of the vaccine's efficacy and safety in a living organism. Studies using mouse models have shown that peptide-based vaccines can induce potent anti-tumor immune responses. For example, a study involving a nanoliposomal

vaccine containing long multi-epitope peptides demonstrated significant tumor growth reduction and increased lifespan in HER-2+ TUBO-tumored mice (Zamani et al., 2020). This study highlighted the importance of using a suitable delivery system, such as liposomes, to enhance the vaccine's potency and induce strong immune responses.

Moreover, the combination of peptide vaccines with other immunotherapeutic agents, such as checkpoint inhibitors, has shown promising results in animal models. This combinatorial approach can help overcome the immunosuppressive tumor microenvironment, which is a significant barrier to the efficacy of peptide-based vaccines (Parmiani et al., 2014; Liu et al., 2021; Buonaguro and Tagliamonte, 2023). For instance, the use of checkpoint inhibitors like anti-CTLA-4 and anti-PD-1/PD-L1 in combination with peptide vaccines has led to dramatic tumor shrinkage and prolonged survival in various cancer models (Khong and Overwijk, 2016; Bezu et al., 2018).

4.3 Translational research

Translational research bridges the gap between preclinical studies and clinical applications, focusing on the practical implementation of peptide-based vaccines in treating oral cancer. One of the key challenges in this field is the limited clinical success of peptide vaccines despite encouraging preclinical data. This discrepancy is often due to the complex tumor microenvironment and the need for personalized approaches to vaccine design (Hirayama and Nishimura, 2016; Buonaguro and Tagliamonte, 2023).

Recent advancements in genetic and bioinformatic analysis have facilitated the identification of neoantigens, which are mutation-derived antigens unique to individual tumors. Personalized peptide-based vaccines targeting these neoantigens have shown potential in eliciting robust anti-tumor immune responses10. Additionally, the combination of peptide vaccines with immune checkpoint blockade therapies has been explored to enhance their clinical efficacy. For example, a phase II clinical trial involving melanoma patients treated with peptide-based vaccination and interferon alpha showed encouraging relapse-free and overall survival rates, justifying further evaluation in clinical trials (Figure 2) (Urbani et al., 2020).

Preclinical studies on peptide-based vaccines for oral cancer have demonstrated their potential in eliciting strong immune responses and reducing tumor growth. In vitro studies provide insights into the mechanisms of action, while animal models offer a more comprehensive understanding of the vaccine's efficacy and safety. Translational research focuses on overcoming the challenges associated with clinical application, emphasizing the need for personalized approaches and combinatorial therapies to enhance the efficacy of peptide-based vaccines in treating oral cancer.

5 Clinical Outcomes of Peptide-Based Vaccines in Oral Cancer

5.1 Overview of clinical trials

Peptide-based vaccines have been extensively studied in various cancer types, including oral cancer, due to their ability to elicit specific immune responses against tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs). Clinical trials have demonstrated the potential of these vaccines to induce robust immune responses and improve clinical outcomes. For instance, a phase I study on metastatic colorectal cancer patients using a combination of five therapeutic epitope-peptides showed promising safety and immunological responses, with some patients achieving stable disease and even complete response (Hazama et al., 2014). Similarly, a phase II randomized controlled trial on castration-resistant prostate cancer (CRPC) patients demonstrated that personalized peptide vaccine (PPV) immunotherapy significantly prolonged progression-free survival (PFS) and overall survival (OS) compared to dexamethasone alone (Yoshimura et al., 2016).

5.2 Efficacy results

The efficacy of peptide-based vaccines in clinical settings has been a focal point of research. In a study involving patients with advanced non-small-cell lung cancer (NSCLC), the universal cancer peptide-based vaccine (UCPVax) showed a 1-year overall survival (OS) rate of 34.1%, with a median OS of 9.7 months. Immune

responders had significantly better outcomes, with a 1-year progression-free survival (PFS) of 17.2% and a median OS of 11.6 months (Adotévi et al., 2022). Another study on metastatic colorectal cancer patients using a 7-peptide cocktail vaccine combined with oral chemotherapy reported partial responses in some patients and stable disease in others, indicating the potential of peptide vaccines to control tumor progression (Okuno et al., 2014).

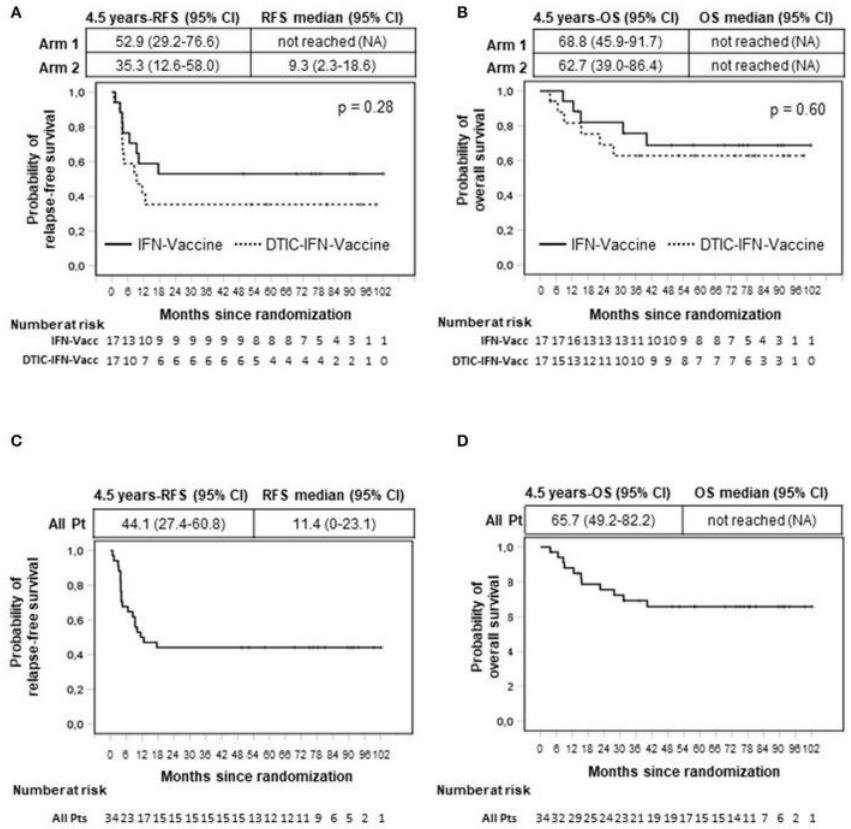

Figure 2 DTIC-IFN N Vaccine Trial Randomization Chart and Sample Size (Adopted from Urbani et al., 2020)

Image caption: Intention-to-treat analysis of relapse-free (RFS) (A,C) and overall survival (OS) (B,D) by Kaplan–Meier method. All enrolled patients were included in the analysis (n=34). Months are calculated since time of randomization. Arm 1 patients (Pt) (n = 17) were treated with vaccination with Melan-A and NY-ESO-1 peptides (Vaccine) and interferon-α2b (IFN). Arm 2 patients (n = 17) received the same treatment of arm 1 patients with the addition of dacarbazine (DTIC) pretreatment. (A,B) Comparison between arms. (C,D) All patients (n=34). p value by log-rank test (Adopted from Urbani et al., 2020)

5.3 Safety and side effects

Safety is a critical aspect of any cancer therapy, and peptide-based vaccines have generally shown a favorable safety profile. In the phase I study on metastatic colorectal cancer, the combination vaccine treatment was well tolerated, with no severe treatment-associated systemic adverse events reported. The most common side effects were mild, such as injection site redness and induration6. Similarly, the phase II trial on CRPC patients reported that PPV immunotherapy was well tolerated, with no significant adverse events compared to the control group (Yoshimura et al., 2016). The UCPVax study also confirmed the safety of the vaccine, with no dose-limiting toxicities observed (Adotévi et al., 2022).

5.4 Case studies

Case Study 1: metastatic colorectal cancer

A phase I clinical trial was conducted to evaluate the safety and immunological response of a combination vaccine treatment using five novel HLA-A*2402-restricted peptides in patients with advanced colorectal cancer6. Eighteen patients who had failed standard therapy were enrolled in the study. The vaccine treatment was well tolerated, and dose-dependent induction of peptide-specific cytotoxic T lymphocytes was observed. One patient

achieved complete response, and six patients revealed stable disease for 4 to 7 months. The median overall survival time (MST) was 13.5 months. Patients with induction of cytotoxic T lymphocytes specific to three or more peptides had significantly better prognosis (MST; 27.8 months) compared to those with poorer immune responses (MST; 3.7 months) (Hazama et al., 2014).

Case Study 2: castration-resistant prostate cancer

A phase II randomized controlled trial was conducted to evaluate the safety and clinical outcomes of personalized peptide vaccine (PPV) immunotherapy in chemotherapy-naive castration-resistant prostate cancer (CRPC) patients2. Thirty-seven patients received peptide vaccinations, and 35 received dexamethasone alone. The primary endpoint was PSA progression-free survival (PFS), which was significantly longer in the vaccination group than in the dexamethasone group (22.0 vs 7.0 months; p=0.0076). Median overall survival (OS) was also significantly longer in the vaccination group (73.9 vs 34.9 months; p=0.00084). The study concluded that PPV immunotherapy was well tolerated and associated with longer PSA PFS and OS in men with chemotherapy-naive CRPC (Table 1) (Yoshimura et al., 2016).

Table 1 Summary of the clinical results (Adopted from Yoshimura et al., 2016)

-	Vaccination and Dex n=37	Dexalone n=36
PSA response rates (%)	-	
>50%decline	22 (59.6)	19 (54.3)
>90%decline	5 (13.5)	7 (20.0)
PSA progression-free survival,median,d	665	210
Median 95%CI	277-1054	156-264
Hazard ratio(95%Cl)	0.39 (0.22-0.68)	
p value	0.0076	
Time to chemotherapy initiation, median, d	1576	719
Median 95% CI	1203-1949	634-804
Hazard ratio (95% Cl)	0.50 (0.25-1.003)	
p value	0.047	
Overall survival, median, d	2219	1054
Median 95%CI	1546-2892	769-1340
Hazard ratio(95% CI)	0.41(0.21-0.83)	
p value	0.00084	
Cancer death	10	25

Table caption: CI=confidence interval; Dex=dexamethasone; PSA=prostate-specific antigen

Case Study 3: Non-Small-Cell lung cancer

A phase Ib/IIa trial was designed to test the safety, immunogenicity, and efficacy of a universal cancer peptide-based vaccine (UCPVax) in patients with metastatic non-small-cell lung cancer (NSCLC)3. Fifty-nine patients received UCPVax, and no dose-limiting toxicity was observed. The vaccine induced specific CD4+ T helper 1 response in 56% and 87.2% of patients after the third and sixth doses, respectively. Twenty-one patients achieved disease control (stable disease, n=20; complete response, n=1). The 1-year overall survival (OS) was 34.1%, and the median OS was 9.7 months. The study concluded that UCPVax was highly immunogenic and safe, providing an interesting 1-year OS rate in heavily pretreated advanced NSCLC (Adotévi et al., 2022).

These case studies highlight the potential of peptide-based vaccines in improving clinical outcomes for cancer patients, including those with oral cancer. The favorable safety profile and ability to induce robust immune responses make these vaccines a promising approach in cancer immunotherapy (Parmiani et al., 2014; Liu et al., 2021; Abd-Aziz and Poh, 2022).

6 Challenges and Limitations

6.1 Immunogenicity and HLA restriction

One of the primary challenges in the development of peptide-based vaccines for oral cancer is ensuring sufficient immunogenicity and overcoming HLA restriction. Immunogenicity refers to the ability of a vaccine to provoke an immune response, which is crucial for the vaccine's effectiveness. However, peptide-based vaccines often face limitations in this area. The immunogenicity of these vaccines can be influenced by the selection of epitopes, the use of adjuvants, and the delivery system employed (Parmiani et al., 2014; Gallou et al., 2016; Tardón et al., 2019; Abd-Aziz and Poh, 2022).

HLA restriction is another significant hurdle. Human leukocyte antigen (HLA) molecules play a critical role in the immune system by presenting peptide antigens to T cells. However, the variability in HLA molecules among individuals means that a peptide vaccine effective in one person may not be effective in another. This necessitates the identification and inclusion of epitopes that can bind to a broad range of HLA molecules to ensure a wider applicability of the vaccine (Lin et al., 2014; Peres et al., 2015; Liu et al., 2021; Jiang et al., 2022). For instance, the use of multi-epitope peptides and the inclusion of pan-HLA-DR epitopes have been explored to address this issue (Zamani et al., 2020).

6.2 Manufacturing and scalability

The manufacturing and scalability of peptide-based vaccines present another set of challenges. The production of synthetic peptides requires precise and high-quality synthesis processes, which can be both time-consuming and costly. Ensuring the consistency and purity of the peptides is crucial for the vaccine's safety and efficacy (Hazama et al., 2014; Abd-Aziz and Poh, 2022).

Scalability is also a concern, particularly when moving from laboratory-scale production to large-scale manufacturing required for clinical use. The complexity of producing multi-epitope peptides and the need for stringent quality control measures can further complicate the scaling-up process. Additionally, the formulation of these vaccines often involves the use of adjuvants and delivery systems, which must be compatible with large-scale production methods (Malonis et al., 2019; Zamani et al., 2020).

6.3 Regulatory and ethical considerations

Regulatory and ethical considerations are critical in the development and deployment of peptide-based vaccines for oral cancer. Regulatory agencies, such as the FDA, have stringent requirements for the approval of new vaccines, including extensive preclinical and clinical testing to demonstrate safety and efficacy. The regulatory pathway for peptide-based vaccines can be particularly challenging due to the need for personalized approaches and the inclusion of novel adjuvants and delivery systems (Bezu et al., 2018).

Ethical considerations also play a significant role, especially in the context of personalized medicine. The development of personalized peptide vaccines involves the identification of patient-specific neoantigens, which raises concerns about privacy and the use of genetic information. Additionally, the cost of personalized vaccines can be prohibitive, potentially limiting access to these therapies for certain patient populations (Peres et al., 2015; Liu et al., 2021).

In conclusion, while peptide-based vaccines hold significant promise for the treatment of oral cancer, several challenges and limitations must be addressed to realize their full potential. Ensuring sufficient immunogenicity and overcoming HLA restriction, addressing manufacturing and scalability issues, and navigating regulatory and ethical considerations are critical steps in the development of effective and widely accessible peptide-based vaccines for oral cancer. Continued research and innovation in these areas are essential to overcome these hurdles and improve clinical outcomes for patients.

7 Future Directions

7.1 Innovations in peptide vaccine design

The design of peptide-based vaccines for oral cancer has seen significant advancements, yet there remains a need for further innovation to enhance their clinical efficacy. One critical area of focus is the selection of optimal antigen targets. Tumor-associated antigens (TAAs) and neoantigens have been identified as promising targets due to their ability to elicit strong immune responses (Nelde et al., 2021). Additionally, the incorporation of adjuvants and nanomaterials has been shown to optimize the immune response, thereby improving the clinical application of these vaccines (Liu et al., 2021).

Recent studies have highlighted the potential of personalized peptide-based vaccines, which are tailored to the unique antigenic profile of an individual's tumor. This approach leverages neoantigens, which are specific to the tumor and not present in normal tissues, thus minimizing the risk of autoimmunity and enhancing the specificity of the immune response (Hirayama and Nishimura, 2016; Abd-Aziz and Poh, 2022). Moreover, the use of cell-penetrating peptides (CPPs) to enhance antigen delivery into the cross-presentation pathway of dendritic cells has shown promise in improving vaccine efficacy (Wylie et al., 2016).

Another innovative strategy involves the modification of peptide sequences to increase their immunogenicity. This can be achieved through the alteration of amino acid sequences to enhance binding affinity to major histocompatibility complex (MHC) molecules, thereby improving T cell activation (Parmiani et al., 2014; Jiang et al., 2022). The development of predictive biomarkers to identify patients who are most likely to respond to peptide-based vaccines is also a crucial area of research, as it can help tailor treatments to individual patients and improve overall outcomes (Nelde et al., 2021).

7.2 Combination therapies

Combining peptide-based vaccines with other therapeutic modalities has emerged as a promising strategy to enhance their efficacy. One such approach is the combination with immune checkpoint inhibitors, which can help overcome the immunosuppressive tumor microenvironment and enhance the anti-tumor immune response (Hirayama and Nishimura, 2016; Obara et al., 2018; Tardón et al., 2019). Immune checkpoint inhibitors, such as those targeting CTLA-4, PD-1, and PD-L1, have shown significant clinical benefits when used in conjunction with peptide-based vaccines (Hirayama and Nishimura, 2016; Tardón et al., 2019).

Additionally, the combination of peptide-based vaccines with chemotherapeutic agents or other immunotherapies, such as adoptive T cell transfer, has demonstrated improved clinical outcomes in various cancer types (Liu et al., 2021; Abd-Aziz and Poh, 2022). These combination therapies can work synergistically to enhance the overall anti-tumor response, reduce tumor burden, and improve patient survival rates.

Another promising combination strategy involves the use of adjuvants that can boost the immune response to the vaccine. For instance, Montanide ISA-51 has been identified as an effective adjuvant that can enhance the clinical response to peptide-based vaccines (Jiang et al., 2022). The use of adjuvants in combination with peptide vaccines can help to overcome the limited potency of current adjuvants and improve the overall efficacy of the vaccine (Tardón et al., 2019).

7.3 Improving clinical trial designs

To fully realize the potential of peptide-based vaccines for oral cancer, it is essential to improve the design of clinical trials. One key aspect is the stratification of patients based on predictive biomarkers, which can help identify those who are most likely to benefit from the vaccine (Nelde et al., 2021). This personalized approach can enhance the efficiency of clinical trials and increase the likelihood of achieving positive outcomes.

Another important consideration is the optimization of vaccination schedules and dosing regimens. Studies have shown that the timing and frequency of vaccine administration can significantly impact the immune response and clinical efficacy (Nelde et al., 2021; Abd-Aziz and Poh, 2022). Therefore, it is crucial to conduct thorough investigations to determine the optimal vaccination protocols for different patient populations.

Furthermore, the integration of advanced technologies, such as next-generation sequencing and bioinformatics, can facilitate the identification of novel neoantigens and the development of personalized vaccines (Hirayama and Nishimura, 2016; Jiang et al., 2022). These technologies can also aid in the monitoring of immune responses and the identification of potential biomarkers for treatment response.

It is important to conduct larger, multi-center clinical trials to validate the efficacy and safety of peptide-based vaccines. These trials should include diverse patient populations to ensure the generalizability of the findings and to identify any potential differences in response based on genetic or environmental factors (Liu et al., 2021; Obara et al., 2018). By addressing these key areas, future clinical trials can provide more robust evidence for the clinical application of peptide-based vaccines in the treatment of oral cancer.

8 Concluding Remarks

Peptide-based vaccines have emerged as a promising approach in cancer immunotherapy, including for oral cancer. These vaccines are designed to elicit specific immune responses against tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) by stimulating CD8+cytotoxic T cells and CD4+helper Tcells. Despite initial challenges in clinical efficacy, recent advancements have shown that modifying peptide sequences to enhance immunogenicity and combining vaccines with adjuvants or other immunotherapies can significantly improve outcomes. Personalized peptide-based vaccines, which are tailored to an individual's tumor antigen repertoire, have also shown promise in enhancing antitumor responses.

The implications of peptide-based vaccines for oral cancer treatment are substantial. These vaccines offer a targeted approach that can potentially reduce the side effects associated with conventional therapies. By specifically targeting TAAs or TSAs, peptide-based vaccines can induce a robust and specific immune response, minimizing damage to healthy tissues. The combination of peptide vaccines with immune checkpoint inhibitors or other therapeutic agents has shown enhanced efficacy, suggesting that a multi-faceted approach could be particularly beneficial for oral cancer patients. Additionally, the development of novel delivery systems, such as liposomal formulations, has been shown to improve the potency and effectiveness of these vaccines, which could be crucial for overcoming the immunosuppressive tumor microenvironment often seen in oral cancers.

Peptide-based vaccines represent a significant advancement i n the field of cancer immunotherapy, with the potential to transform the treatment landscape for oral cancer. While there are still challenges to be addressed, such as optimizing vaccine formulations and overcoming tumor-induced immunosuppression, the progress made thus far is encouraging. Future research should focus on the development of more effective adjuvants, the identification of optimal peptide targets, and the integration of peptide vaccines with other therapeutic modalities. Personalized approaches, leveraging the unique antigenic profiles of individual tumors, are likely to play a critical role in the success of peptide-based vaccines. As our understanding of the immune system and tumor biology continues to evolve, peptide-based vaccines hold great promise for improving clinical outcomes and providing a more targeted, less toxic treatment option for oral cancer patients.

Acknowledgments

The authors extend sincere thanks to two anonymous peer reviewers for their feedback on the manuscript.

Conflict Of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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