

Tumor Vaccine For Oral Cancer: Prospects And Challenges In Dentistry

Abstract

Oral cancer is one of the major reasons for morbidity and mortality worldwide. Despite significant advances in radiation, surgery and chemotherapy, substantial gap remains in its effective control. Even with all recent advances, the overall five-year survival rate for oral cancer has remained status quo at around 55% and hence, a need for effective vaccine has been felt for long that could confer long-term immunity and have a huge impact in control of this deadly disease. We did a retrospective literature search with key terms "Tumors Vaccines" AND "Oral Cancers" AND "Dentistry" through Pub Med, MEDSCAPE, MICROMEDEX, relevant immunology, dental and medicine journals and this was done independently by the authors. Majority of tumor vaccine research in dentistry is limited to Human Papilloma Virus (HPV) vaccines. However these are more focused on cervical cancer, with oral malignancy as only one of the secondary outcomes. It has been observed that HPV has a definitive role in oral cancers and these vaccines could have a positive impact in prevention of its ever-increasing incidence, though gray areas in research like optimal dosing schedule, efficacy in men, duration of protection and oral cancer specific studies remain unanswered. Emergence of second generation tumor vaccines against oral cancer does seem promising. There is a need to sensitize dental professionals with the latest advancement in tumor vaccines. A subtle shift from bench side research to bed side availability of an effective tumor vaccine in dentistry armamentarium does not seem to be a distant

Key Words

Oral cancer, Tumor vaccine, Human Papilloma Virus, Immunization, Dentistry

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy and a major cause of cancer morbidity and mortality globally (1). High incidence of these cancers is seen in the Indian subcontinent, Australia, few European countries (Netherlands, France, Switzerland), Brazil and South Africa (2). Studies show male preponderance in France but a female predominance in India and Pakistan (3). Cancers of the mouth and the tongue predominate in developing countries whereas pharyngeal cancers are common in developed countries including Central and Eastern Europe. The mainstay of management remains surgery, radiation and chemotherapy. However, despite advances in screening tools, imaging technology and access to primary care physicians, a considerable percentage of patients present with advanced stage disease. Survival of oral cancer has not improved in the past 30 years and hence there is still a substantial gap in the management of oral cancer and a need for an effective vaccine to prevent oral cancer cannot be overlooked. Recent developments in the field of immunology have resulted in a vaccine to treat patients with HPV against cervical cancer. HPV is

accepted as an etiological factor for oral and pharyngeal cancers. Numerous trials have studied the prevalence of HPV in OSCC and a largest study on this aspect calculated the average to be 4% for cancers of the oral cavity and 18% for oro-pharyngeal cancers (4). Kreimer et al (5) showed HPV-16 was the predominant type in 87% and 68% cases of HPV infected oro-pharyngeal and oral cancers respectively. Hence a possible reduction in OSCC as a result of widespread vaccination against HPV appears promising, as a good proportion of the infection is caused by HPV types and therefore potentially preventable.

Tumor vaccine research

HPV is non-enveloped with a 8.0 kb circular genome that encodes two structural proteins (L1 and L2) that form the viral capsid and more than 100 strains have been identified (6). The virus gains entry through a micro trauma to the superficial epithelial layer and goes on to invade the basal epithelial layer. It has the ability to evade the immune system and thereby limiting gene expression and viral replication to the suprabasilar layers (7). The HPV virus appears to have a latency period of 10 years or more before malignant transformation occurs. The discovery,

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development and testing of the two highly promising HPV vaccines (**Table 1**)

is a major breakthrough in modern preventive medicine (8-10). HPV vaccine is a non-infectious, subunit, viral vaccine based on the L1 major capsid protein. When expressed in eukaryotic cells, L1 proteins are able to self-assemble into virus-like particles (VLP) that are very similar to authentic virions and can induce high titers of antibodies able to prevent infection by native virions (9). VLPs can be produced in both yeast cells and baculovirus-infected insect cells. The VLP based vaccine is type-specific and can therefore target the HPV genotype most commonly associated with the development of oral cancer (7). HPV types 16 and 18 are responsible for majority of oral cancers and so, monovalent and/or polyvalent vaccines, which target one or more of these types would provide the most beneficial and efficient protection against HPV (11). Both vaccines are administered as an intramuscular series of three injections over a six-month period.

Efficacy of tumor vaccine against oral cancer

Available HPV vaccines, at present are prophylactic and not therapeutic.

Table 1. Currently available HPV vaccines

Vaccines against HPV	Description	Major Clinical studies	Dosing schedule and availability	Adverse events / Precautions
Bivalent HPV- 16/18 (Cervarix by GlaxoSmithKline)	Each 0.5 ml dose contains 20 µg each of HPV-16 L1 and HPV-18 L1 proteins	Harper et al., ²⁰ : Initial follow up of 2.2 years and subsequent median follow-up of 4 years showed 100% efficacy	Intramuscularly in the deltoid region at 0, 1 and 6 months interval available as 0.5 ml suspension in a pre-filled syringe/vials.	Very common: injection site reactions, myalgia, and headache. Common: gastrointestinal disorders, arthralgia, fever. Uncommon: upper respiratory tract infections, dizziness Must be stored at 2-8° C US FDA Pregnancy category : B (However, limited data available) Not evaluated in males Limited data in breastfeeding
Quadrivalent HPV-6/11/16/18 (Gardasil by Merck)	Each 0.5 ml dose contains 20µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein	Protocol 007, FUTURE I and FUTURE II studies: Remarkable efficacy in Phase II and Phase III trials (90-100% efficacy)	Intramuscularly 0.5 ml doses at 0, 2 and 6 months interval. Vaccine is available as a sterile suspension for injection in a single-dose vial or a pre-filled syringe.	Very common: injection site reactions. Common: fever, dizziness, nausea. Uncommon: bronchospasm, arthritis, pelvic inflammatory disease, headache. Must be stored at 2-8° C US FDA Pregnancy category : B (however, limited data, not recommended for use in pregnancy) Lactating women can receive HPV vaccine when benefit outweigh the possible risk Not licensed for use among males Not licensed for use among males

Numerous studies done till date discuss the effect of HPV vaccines against cervical cancer alone and do not address the issue related to tumour vaccine specifically for oral cancer. It is surprising indeed, that though OSCC is a common cancer there are only a handful of studies dealing on this issue. One of the recent studies investigated immunomodulatory activity of autologous tumour cell vaccine from oral cancer patients *ex vivo* by lymphoproliferation assay and two color flow cytometry. Vaccine treatment lead to 10-fold higher proliferation of lymphocytes compared to untreated controls (12). This finding of lymphocyte proliferation is definitely a positive prognostic factor for oral cancer patients. Another study 'throws up' a promise in the prevention of HPV associated oral cancer with the help of L1 DNA vaccines (13). Due to lack of further studies pertaining to vaccines in oral cancer, the exact impact of HPV in prevention of oral and oro-pharyngeal cancers and other benign lesions is not known. As the overall 5-year survival rate for OSCC is only approximately 55%, if a vaccine could confer long-term immunity and reduce the incidence of oral cancer, it will have a huge

impact on the society. Also, HPV is considered to be a sexually transmitted due to abnormal sexual practices. Sex education, improvement in personal hygiene and vaccination in high risk groups can also add on to bring down the incidence of oral cancer (14). Dentists can play a crucial role

through effective counseling pertaining to safe sexual practice and oral hygiene.

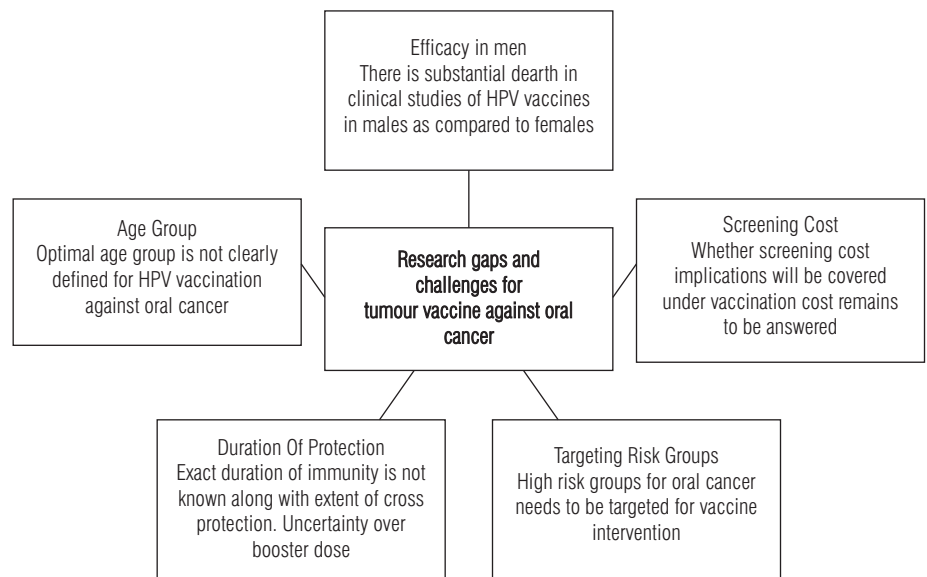
Gaps in knowledge and research

There is a substantial gap in knowledge and research when tumour vaccines move from bench side to bed side. Though an optimal age group for vaccination is not clearly defined, immunological bridging studies have documented better serological responses to the quadrivalent vaccines among 9-15 year old females than among the older group (15). US FDA has recently approved the quadrivalent vaccine for use in women between 9-26 years of age (6). Till to date, there is no data focusing the efficacy of HPV vaccine in males. However, the burden of HPV-16 associated penile, anal and oropharyngeal cancers in men are not significant and considerably less than the HPV 16/18 associated cervical disease in women (16). Though HPV vaccine generates VLPs that induce strong immune response that is protective against persistent HPV infection, the durability of response imparted by HPV vaccine and the timing of a booster dose is not clear and can be determined only by monitoring antibody levels to HPV infections in immunized subjects (17).

Some of the overlooked areas in research include

- the extent of cross-type neutralization induced by VLPs in in-vitro assays
- immune protection, status of immune response post-vaccination
- to determine if herd immunity is induced
- the exact duration of protection, degree and duration of cross protection against the types not included in the vaccine

Figure 1: Tumour vaccine against oral cancer: the challenges



- (e) determination of safety and efficacy of the vaccines in elderly, HIV positive and other immunocompromised individuals
- (f) determining the impact of vaccination on prevalent infections especially the anogenital and oral infections.

Figure 1 summarizes the research gaps and challenges ahead in vaccine research against oral cancer.

Clinical evaluation and endpoints for tumor vaccines

It is important to know the endpoints for judging the therapeutic efficacy of HPV vaccines against oral cancer. Vital prerequisites for all vaccines as endpoints are (a) immunogenicity (B and T cell responses), (b) reactogenicity (local and systemic reactions), (c) safety (short and long term adverse events) and (d) protection (clinical trials efficacy and effectiveness in population use). Clinical endpoints can be assessed through physical examination, by cytology through Papanicolaou testing or histologically through biopsy sampling. Endpoints for HPV vaccine against cervical cancer are well defined, but for oral cancer it remains under review. All adverse events occurring during the clinical trials with HPV vaccines are registered and their frequency is determined. Causality between the adverse events and vaccination are evaluated (18). Psychosocial impacts are often neglected as a part of screening the patients with oral cancer. Decrease in anxiety may be a positive benefit of vaccine administration for which definite endpoint need to be defined (19, 20). National immunization advisory committees in various countries can play a crucial role while facilitating HPV vaccine administration against oral cancer.

Conclusion

Although there is considerable lack of tumour vaccine studies focusing on oral cancer, the substantial benefit of preventing oral cancers through vaccine administration cannot be overlooked. Need for research in this area with focus on efficacy, safety and post-marketing surveillance is crucial. Multidisciplinary approach with dentists in particular, needs to be sensitized with the latest advancement in tumour vaccine research. A subtle shift from bench side research to bed side availability of an effective tumour vaccine in the armamentarium of dental professionals does not seem to be a distant dream.

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