

Immunotherapeutic Approach to Squamous Cell Carcinoma of the Head and Neck

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Abstract

Head and neck cancers make up of 3-5% of cancer diagnoses in the United States. The most common occur in the squamous cells of the head and neck. Immunotherapy is an alternative to chemotherapy and radiation therapy to treat cancer. It is utilized by stimulating one's own immune system to fight the tumor. Another way to utilize immunotherapy is by giving someone synthetic immune system proteins to fight the cancer. In this paper, we discuss the pathophysiology of squamous cell head and neck cancer, the active molecules involved in immunotherapy, as well as potential ways to fight these cancers using immunotherapy.

Keywords: Head and neck cancer; Immunotherapy; Epidermal growth factor receptor; Kinase inhibitor; Monoclonal antibody; Cytokine; Vaccine; T cell

Introduction/Epidemiology

Head and neck cancer arises in regions such as the lips, sinuses, nasal cavity, throat, salivary glands, mouth, or larynx [1]. There are various types of cancers that occur in the head and neck, but the most common cancer is squamous cell carcinoma of the head and neck (HNSCC). The HNSCC starts in the flat cell layer of the epithelium that lines the structures of the upper aero digestive tract. This includes the voice box (larynx), throat (pharynx), and mouth (oral cavity). Head and neck cancer accounts for around 3-5% of all the cancers in the United States [2]. In the year 2014, it was estimated that 55,070 new cases (40,220 male and 14,850 female) of head and neck cancer were diagnosed. In the same year, 12,000 deaths (8,600 male and 3,400 female) of the disease were also reported in the United States [3]. The 5-year survival rate of head and neck cancer patients is about 40-50%. [2] In 2008, the worldwide, age-standardized rate of incidence was 5.9 per 100,000 and the mortality rate was 3.3 per 100,000 for oropharyngeal cancer [4]. That includes different types of histopathologic and genetic characteristics. Currently, the ratio of males to females diagnosed with oral cavity and pharyngeal cancers is about 3:1 [5]. The availability of newer technology in diagnosis helps in early detection of head and neck cancer and is a primary requirement for the management of disease.

Head and neck cancer commonly starts in the squamous cells that line the moist, mucosal surfaces within the head and neck (throat, nose, and mouth) [1]. Tobacco (chewing or smoking), HPV infection and alcohol are the most important risk factors for head and neck cancers, particularly cancers of the larynx, hypo pharynx, oropharynx, and oral activity [6-12]. Current studies state that the HPV infection (HPV-16 and -18) is liable for HNSCCs and is presently the leading cause of oropharyngeal SCC (particularly squamous cell carcinoma (SCC) of the tonsils and the base of the tongue) [12].

The most common symptoms of head and neck cancer are frequent headache, trouble hearing, tinnitus, pain in the neck and mouth, pain when swallowing (odynophagia), trouble speaking or breathing, swelling of the jaws, unusual bleeding, and a red or white patch

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on tongue, gums, or lining of the mouth [1]. Other sign and symptoms, such as cough, pain in the ear or behind the sternum, weight loss, change in the voice, lump in the back of the mouth, neck, or throat, and a persistent sore throat may be due to oropharyngeal cancer [1].

Pathophysiology and Molecular Basis of Head and Neck Cancer

HNSCC arises from a common premalignant progenitor followed by the outgrowth of clonal populations. This is associated with cumulative genetic alterations and phenotypic progression to the invasive malignancy [13-15]. These genetic modifications inactivate tumor suppressor genes and activate Proto-oncogenes through gene amplification, point mutations, deletions, and promoter methylation (Table 1). The various microsatellite marker analyses have permitted the description of a genetic progression model for HNSCC. This is based on the regularity of these genetic alterations in the different invasive tumors and preinvasive lesions (Figure1) [14-15]. The most common genetic alteration, the loss of chromosomal region 9p21, is found in 70-80% cases of HNSCC [14, 16-17]. The CDKN2A gene locus, found in chromosome 9p21, encodes two different types of transcripts. They are p14ARF and p16. These are liable for regulating the G1 phase of the cell cycle and also for the degradation of MDM2 of p53. The p16 is frequently inactivated by the homozygous deletion, promoter methylation, or, less commonly, through point mutations [18].

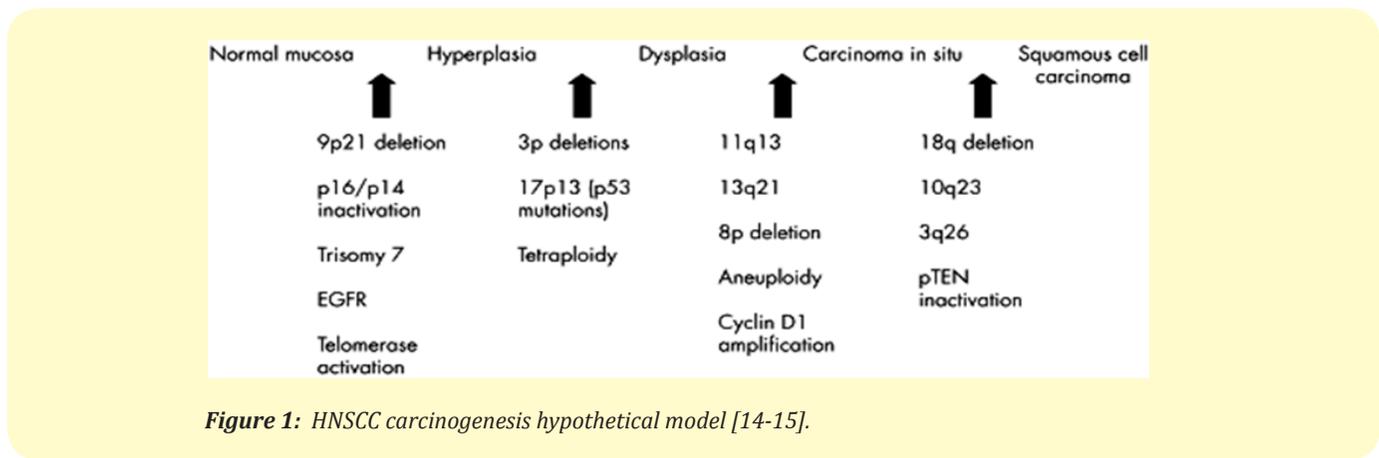


Figure 1: HNSCC carcinogenesis hypothetical model [14-15].

Loss of Heterozygosity (LOH)	Percentage
LOH 9p	70-80%
LOH 3p	60-70%
LOH 17p	50-70%
LOH 11q	30%
LOH 13q	30%
Inactivation of p16ink4A (homozygous deletion, promoter methylation, point mutation)	80%
Inactivation of FHIT and RASSF1A p53 mutation	50-80%
Cyclin D1 amplification	30%

Table 1: Common molecular abnormalities in HNSCC [19].

Immunotherapy of Squamous cell carcinoma of the head and neck

A. Monoclonal Antibody (MABs):

1. **Cetuximab:** [20] it is a FDA approved drug to treat locally advanced HNSCC in combination with radiation therapy. Other indications are metastatic HNSCC either in combination with platinum based therapy with 5-FU, or as a single agent in recurrent or metastatic

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HNSCC. The most common adverse events of Cetuximab are infection, diarrhea, headache, nail changes, pruritus, and rash. Cetuximab should be permanently discontinued for serious reactions such as hypotension, loss of consciousness, cardiac arrest, and myocardial infarction. Cetuximab should not be administered to the patients with congestive heart failure (CHF), interstitial lung disease (ILD), coronary artery disease, or arrhythmias. Patients with hypokalemia, hypocalcaemia, and hypomagnesaemia should be closely monitored.

2. Trastuzumab: [21] this is a recombinant, humanized, monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2) that is currently in a phase I/II clinical trial. After binding to HER2 on the tumor cell surface, trastuzumab induces an antibody-dependent, cell-mediated cytotoxicity against tumor cells that over express HER2, which is over expressed by many adenocarcinomas. It is particularly over expressed in breast adenocarcinomas.

B. Kinase Inhibitor

There are no tyrosine kinase inhibitors that have been approved by the FDA for head and neck cancer. However, the drug that is under clinical trials in phases I-III is shown in Table 2 below.

Erlotinib: This is a quinazoline derivative with antineoplastic properties. Competing with adenosine triphosphate, erlotinib reversibly binds to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

Drug	Clinical trial identifier number	Phase	Study design	Target
Erlotinib	NCT00954226	Phase I	Randomized, Open label, Safety/Efficacy Study	EGFR

Table 2: Tyrosine kinase inhibitor [22].

C. Cytokine therapy

There is no cytokine therapy approved by the FDA for head and neck cancer. However, many cytokines are under clinical trials in phases I- III as in Table 3 below.

1. Leukocyte Interleukin: This is a mixed preparation of interleukin-1/2/6 (IL-1, IL-2, and IL-6), interferon- γ , TNF- α , and different cytokines. The cytokines are chemically identical or similar to the signaling molecules secreted through the various leukocyte cells.

2. IRX-2: It is a cell free mixture that has immunostimulatory activity. The cytokines in IRX-2 are: IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, CSFs, interferon- γ , and TNF- α . All of which play a key role in regulating cellular immunity against various tumor cells.

3. Interleukin-2 Gene: This gene contains the DNA sequence that encodes the protein cytokine interleukin-2 (IL-2). When introduced into tumor cells as the complementary DNA (cDNA) form by a genetically engineered adenovirus vector, the transfected IL-2 cDNA expresses IL-2, which activates antitumoral natural killer cells and elicits an antitumoral, cytotoxic T-cell response, resulting in an inhibition of tumor progression.

Drug	Clinical trial identifier number	Phase	Study design	Target
Leukocyte Interleukin (LI) + CIZ, LI + SOC	NCT01265849	Phase III	Randomized, Open Label, Safety/Efficacy Study	Cancer cells
IRX-2	NCT00210470	Phase II	Safety/Efficacy Study, Open Label	Cancer cells
Interleukin-2 Gene	NCT00006033	Phase II	Open label, Multicenter	Cancer cells

Table 3: Cytokine therapies [23-26].

D. Vaccine Immunotherapy

There are no vaccines currently approved by the FDA for head and neck cancer. However, many vaccines are under clinical trials in phase's I-III as in Table 4 below.

1. **AlloVax:** This is a personalized, anti-cancer vaccine combining chaperone rich cell lysate (CRCL) as a source of tumor antigen prepared from the patient's tumor and AlloStim™ as an adjuvant. The combination of CRCL and AlloStim™ is designed to provide all of the key components necessary to develop a tumor-specific immunity. This creates the inflammatory environment necessary to overcome the HNC immunosuppressive environment while breaking tumor immune tolerance and provision of specific HNC antigens for generation of a specific adaptive anti-tumor response.
2. **INO-3112:** This is an active immunotherapy that targets HPV 16 and 18 and simultaneously expresses IL-12. It is designed to activate *in vivo* immune responses to antigens from high-risk HPV types and eliminate precancerous and cancerous cells displaying these antigens.
3. **ADXS11-001:** It is a cancer vaccine containing a live-attenuated strain of the bacterium, *Listeria monocytogenes* (Lm) encoding human papillomavirus (HPV) type 16 E7 fused to a non-hemolytic listeriolysin O protein with potential immunostimulatory and antineoplastic activities. Upon vaccination, Lm expresses the HPV 16 E7 antigen and activates the immune system to mount a cytotoxic T-lymphocyte (CTL) response against cancer cells expressing HPV 16 E7. This may result in tumor cell lysis. In addition, the Lm vector itself may induce a potent immune response. HPV 16 E7, a cell surface glycoprotein and tumor-associated antigen, is over expressed in the majority of cervical cancer cells.

Drug	Clinical trial identifier number	Phase	Study design	Target
AlloVax	NCT01998542	Phase I, II	Double blind, Safety/Efficacy Study	Cancer cells
INO-3112	NCT02163057	Phase I, II	Non-Randomized, Open label, Safety/Efficacy Study	Cancer cells
ADXS11-001	NCT02002182	Phase II	Non-Randomized, Open label, Safety/Efficacy Study	Cancer cells

Table 4: Vaccine immunotherapies [27-29].

E. Adoptive T Cell Immunotherapy

There are no biologicals currently approved by the FDA for head and neck cancer. The only clinical trial that is in phase I-III is in Table 5 below.

Intra-tumoral T4 immunotherapy: This is an autologous cell therapy in which peripheral blood T-cells are genetically engineered through a retroviral vector to co-express two chimeric receptors, such as T1E28z and 4αβ.

Drug	Clinical trial identifier number	Phase	Study design	Target
Intra-tumoral T4 immunotherapy	NCT01818323	Phase I	Safety Study, Open Label	Cancer cells

Table 5: Adoptive T-cell immunotherapy [30].

Conclusion

The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities and combination therapies (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with chemotherapy in cancer patients are still in the exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper pre-clinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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