# A PHARMACOLOGICAL REVIEW ON HEAD AND NECK CANCER

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**Abstract**

Head and neck cancer are a group of cancers of the mouth, sinuses, nose or throat, where smoking is considered a major risk factor. Symptoms may appear in mouth, sinuses, nose or throat and include a sore or lump that doesn't heal, a persistent sore throat, trouble swallowing and changes in the voice. Prognosis in this type of cancer generally depends on the size of tumor, primary site, causative factor, and presence of local or distant metastases. In general, the prognosis is favourable if diagnosis is early and treatment is timely and appropriate. Treatment includes surgery, radiation therapy or chemotherapy. Staging of tumor can be done using TNM classification and the can be evaluated through RECIST guidelines. Removing risk factors is very much important in preventing this type of cancer, and patients should stop the usage of tobacco and limit alcohol consumption.

A PHARMACOLOGICAL REVIEW ON HEAD AND NECK CANCER

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ABSTRACT: Head and neck cancer are a group of cancers of the mouth, sinuses, nose or throat, where smoking is considered a major risk factor. Symptoms may appear in mouth, sinuses, nose or throat and include a sore or lump that doesn't heal, a persistent sore throat, trouble swallowing and changes in the voice. Prognosis in this type of cancer generally depends on the size of tumor, primary site, causative factor, and presence of local or distant metastases. In general, the prognosis is favourable if diagnosis is early and treatment is timely and appropriate. Treatment includes surgery, radiation therapy or chemotherapy. Staging of tumor can be done using TNM classification and the can be evaluated through RECIST guidelines. Removing risk factors is very much important in preventing this type of cancer, and patients should stop the usage of tobacco and limit alcohol consumption.

KEY WORDS: head and neck cancer, squamous cell carcinoma, tobacco use, lesion, chemotherapy.

INTRODUCTION:

Cancers of the upper nasopharyngeal tract which are collectively known as head and neck cancers, arise from many of sites. These tumours cause major problems in management, and skilled healthcare team is necessary to achieve the highest level of service and research. Previously, surgery and radiotherapy have been widely used in the treatment while, chemotherapy is now increasingly employed but not yet fully established. Current research efforts majorly concentrate on defining the importance of chemotherapy and determining the advantage of unconventional radiation approaches[1]. These malignancies develop in areas responsible for eating, talking, and breathing and are associated with substantial morbidity and mortality despite advances in treatment. We need to understand the advances in head and neck cancer (HNC) management to study the patients across the cancer care continuum. Additionally, the recent Coronavirus Disease 2019 (COVID-19) pandemic has necessitated adaptations to HNC care to accommodate mitigation of COVID-19 risk and ensure timely treatment[2]. Smoking and alcohol abuse are major risk factors for the development of this disease. Majority of the cases are squamous cell carcinomas, and it arises in the oropharynx, oral cavity, hypopharynx, or larynx. HNSCC develops as a result of the both environmental factors and genetic inheritance, and is thus called multifactorial. Human papillomavirus (HPV) is also considered risk factor in about 25% of the disease. Now, there are many surgical procedures, which include robotic surgery, that decreases the tracheotomy rate, and allows a faster oral swallowing recovery and shorter hospital stay[3].

EPIDEMIOLOGY:

Head and neck squamous cell carcinoma (HNSCC) include mucosal squamous

cell carcinomas of the upper aerodigestive region and represents more than 65,000 new cancer cases and 14000 plus cancer-related deaths in the United States annually. Head and neck cancer is mainly associated with smoking and alcohol consumption and have been decreasing in incidence in recent years. In contrast, the primary cause for oropharyngeal SCC is now HPV. The incidence of HPV-associated OPSCC has been exponentially rising, with an annual increase of 3.8% in Caucasian men between for about two and half decades since 1992. The incidence of HPV-positive OPSCC has become more common than HPV-related cervical cancer[4]. A majority of patients can be cured with surgery or radiation with early-stage SCCHN, and those with aggressive disease and those with locally advanced stages, there are mor chances for the cancer to recur[5]. There are about 350,000 deaths yearly which are associated with SCCHN worldwide. In the United States, head and neck cancer cases

accounted for more than 40.000 new cancer cases in 2007, corresponding to 3% of all

new cancer diagnoses in the country. Although there are several advances in treating this cancer, approximately 11,210 head and neck cancer related deaths have been noted during 2007 in the United States[6].

ETIOLOGY & PATHOGENESIS:

Tobacco smoking is considered as a major risk factor for HNSCC, and this is associated with the intensity and duration of smoking habit. The cigarette contains nitrosamines and polycyclic hydrocarbons carcinogens elements that cause toxic effects to genes and therefore may increase the risk of occurrence of disease. These factors are responsible for the alterations in the molecular profile of the individual and cause gene mutations. Alcohol acts as a medium to enhance exposure of the mucosa to carcinogens, thereby increasing cellular uptake of these cancer-causing compounds. The acetaldehyde, can form DNA adducts, which interfere with DNA synthesis and repair. According Marur & Forastiere, tobacco intake along with alcohol consumption increases the HNSCC the risk to 40 times[7]. Figure 1 represents the sites of occurrence of head and neck cancer.

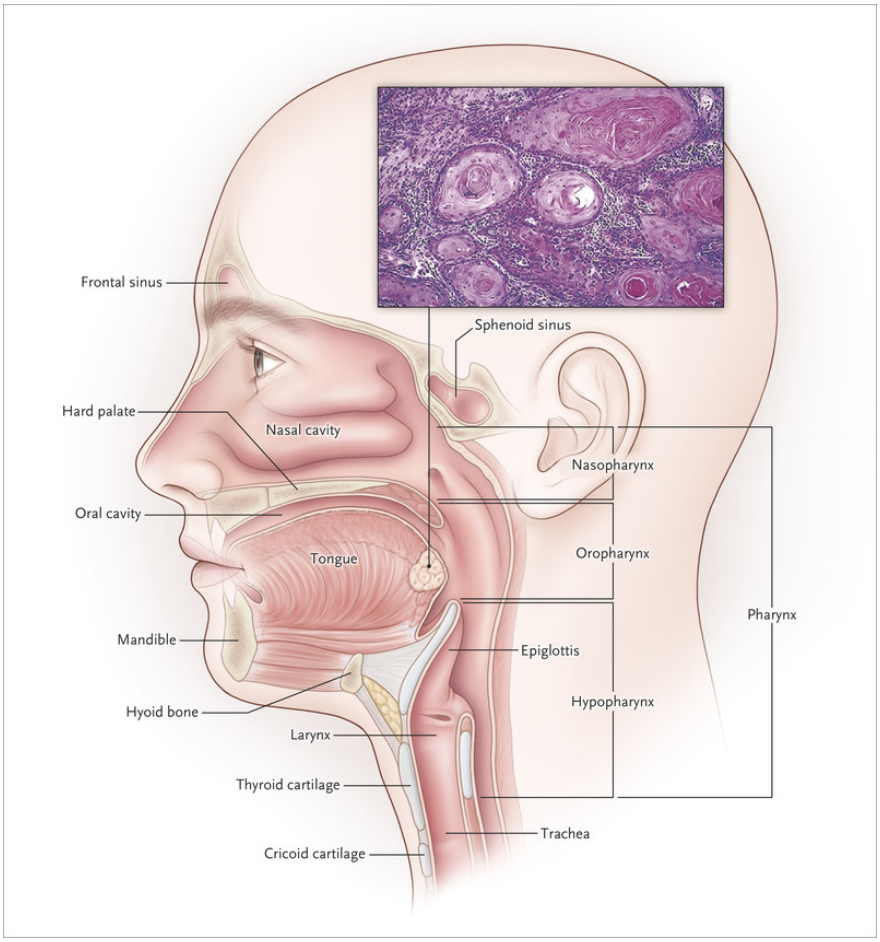


Figure 1: Representation of regions of head and neck cancer[8]

RISK FACTORS:

**Tobacco, alcohol, pan:**

Cigarette smoking and excessive alcohol consumption represent the most important factors for the development of HNSCC and they have a synergistic effect. Reverse smoking is a technique in which the lighted end of the cigarette is kept inside the mouth while smoking is a habit practiced in some areas of India and South America, leads to HNSCC of the hard palate. Chewing of the "betel quid', which is popularly known as 'pan' is also considered an important risk factor for the development of HNSCC of the buccal mucosa and the mandibular buccal sulcus. The habit of betel quid chewing is highly practiced in countries such as India, Pakistan, Bangladesh and Sri Lanka. Although alcohol is not considered to be a carcinogenic agent, heavy alcohol intake along with tobacco use acts synergistically to cause HNSCC.

**Human papilloma virus (HPV):**

Infection with high-risk HPV types (HPV 16, 18. 31 and 33) also

play a role in the pathogenesis of OPSCC. Specifically, HPV type 16 accounts for $> 90\%$ of HPV associated cancer. The shift in biology to HPV over tobacco associated SCC accounts for the improvement in overall survival rates in HNSCC patients

**Other contributing factors:**

Ultraviolet light radiation associated with chronic sun exposure is linked to the development of SCCs on the lips. Other less known risk factors for HNSCC include iatrogenic immunosuppression for solid organ or bone marrow transplant, family history of HNSCC, diet poor in antioxidants and increasing age[9].

**Diagnosis and staging:**

To determine tumor extension, diagnostic imaging is needed:

-Imaging diagnosis before a biopsy avoids misinterpretation from anatomical distortion.

-Computed tomography (CT scan) and Magnetic Resonance Imaging (MRI sacn) are also used in diagnosis. MRI can be beneficial than CT for evaluating tongue, perineural spread, invasion to skull base and intracranial extension.

-CT of chest is preferred, or X-ray is done in early stages.

-Positron emission tomography-CT (PET-CT) is useful in diagnosis of node and metastases and some primary tumors. It is recommended in patients with stage III and IV disease when definitive treatment is indicated.

-Esophagoscopy is carried out in case of dysphagia.

-Histological evaluation is mandatory by primary tumor biopsy or fine needle aspiration (FNA) of lymph nodes.

-Functional evaluation: actions like chewing, swallowing, breathing, odontology and nutritional status are assessed.

-Special evaluations if needed: psychological and social situation assessmet, cessation of smoking or alcohol dependence[10].

The diagnosis of HNSCC can be established by biopsy of the primary tumour. The biopsy method depends upon the location of the tumor. Primary tumours are approached incisional biopsy or excisional biopsy, whereas the suspicious cervical neck mass should be diagnosed with the help of fine needle aspiration (FNA).

A well-differentiated tumour would be similar to the stratified epithelium, with mature-appearing cells organizing into layers with irregular keratinization. A poorly differentiated tumour is characterized by immature cells with nuclear pleomorphism and atypical mitoses, with minimal to no organized keratinization. HPV-negative HNSCCs are moderately or well differentiated, with preservation of stratification and keratinization, whereas HPV-positive HNSCCs are poorly differentiated and even display basaloid morphology on histopathological examination. The histopathological diagnosis of HNSCC can usually be made using haematoxylin and eosin staining. However, in the case of poorly differentiated tumours, immunohistochemistry may be necessary to confirm an epithelial origin[11].

TUMOR RESPONSE EVALUATION (RECIST GUIDELINES)

Evaluation of target lesions:

1. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
2. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
3. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions:

1. Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm).
2. Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
3. Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions.

Measurability of tumour:

Measurable Tumour lesions:

Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

* 10 mm by CT scan (CT scan slice thickness no greater than 5 mm

* 10 mm caliper measurement by clinical exam

* 20 mm by chest X-ray.

Malignant lymph nodes:

To be considered pathologically enlarged and measurable, a lymph node must be <15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

All other lesions, including small lesions and non-measurable lesions and these non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions.

* Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

* Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

* Blastic bone lesions are non-measurable.

Cystic lesions:

* Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions since they are simple cysts.

* Cystic lesions thought to represent cystic metastases can be considered as measurable lesions. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

* Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

STAGING OF TUMOR (TNM CLASSIFICATION)

In the TNM system:

- The T refers to the size and extent of the primary tumor

- The N refers to the number of surrounding lymph nodes that have cancer.
- The M refers to whether the cancer has metastasized.

When your cancer is described by the TNM system, there will be numbers after each letter that give more details about the cancer, which include:

Primary tumor (T)

- TX: Main tumor cannot be measured.
- T0: Main tumor cannot be found.
- T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.

Regional lymph nodes (N)

- NX: Cancer in nearby lymph nodes cannot be measured.
- N0: There is no cancer in nearby lymph nodes.
- N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer.

Distant metastasis (M)

- MX: Metastasis cannot be measured.
- M0: Cancer has not spread to other parts of the body.
- M1: Cancer has spread to other parts of the body.

TNM classification is grouped into following stages:

- Stage 0: Abnormal cells are present but did not spread to surrounding tissue. Also called carcinoma in situ. CIS is not cancer, but it may become cancer in future.
- Stage I, Stage II, and Stage III: Presence of cancer. The higher the number, the larger the tumor and the more the spread into surrounding tissues.
- Stage IV: Spread of cancer to remaining parts of the body.

TREATMENT AND PHARMACOLOGY:

By the end of the 20$^{th}$ century, radiation had just been discovered, and surgical outcomes were of great use due to the lack of antibiotics and the limitations of anaesthesia. Because of these reasons, radiation therapy (RT) had been used as a primary treatment for the first half of

the century. After few decades, due to treatment failures of early RT techniques, led to the

emergency development of primary surgical treatment for most head and neck cancers. Subsequent advancements in RT improved cure rates and decreased treatment failures.

Today, RT remains an important option in early-stage cancers and plays an

important role in the adjuvant setting. Recently, combinations of chemotherapy and

RT have been used majorly for advanced-stage cancers, both for primary and adjuvant

treatment. Finally, targeted molecular therapies have been developed that bring out new options in managing of HNSCC, which may further improve survival rates[12]. Figure 2 represents the treatment options involving chemotherapy for locally advanced squamous cell carcinoma of the head and neck.

**Hosted file**

`image2.emf` available at https://authorea.com/users/730527/articles/710166-a-pharmacological-review-on-head-and-neck-cancer

Figure 2: Treatment options involving chemotherapy for locally advanced squamous cell carcinoma of the head and neck.[13]

MOST COMMON CHEMOTHERAPEUTIC REGIMENS:

Table 1 represents the most common chemotherapeutic regimens.

| chemotherapy | Dose, frequency and no.of cycles |
|---|---|
| Cisplatin (P) | (Every 3 weeks, RT days 1, 22, 43) P: 100 mg/m2 on day 1 |
| Cetuximab | Loading dose: 400 mg/m2 (4–10 days prior to RT) Maintenance: |
| TPF (TAX 324) Docetaxel (T) Cisplatin (P) 5-FU (F) | (Every 3 weeks for 3 cycles) T: 75 mg/m2 on day 1 P: 100 mg/m |
| TPF (European) Docetaxel (T) Cisplatin (P) 5-FU (F) | (Every 3 weeks for 4 cycles) T: 75 mg/m2 on day 1 P: 75 mg/m2 |
| Cisplatin (P) 5-FU (F) | P: 100 mg/m2 on day 1 F: 1000 mg/m2 by CI days 1–5 |

Table 1: Most common chemotherapeutic regimens[14]

PHARMACOLOGY OF DRUGS:

CISPLATIN:

- It is hydrolysed intracellularly, producing a highly reactive moiety which causes cross linking of DNA. The favoured site is $N^7$ of guanine residue.
- It is bound to plasma proteins, penetrates tissues and is slowly excreted unchanged in urine.
- Its $t^{1/2}$ is about 72 hours.

CETUXIMAB:

The inhibitor of EGF receptor is a chimeric monoclonal antibody directed to the extracellular domain of the receptor.

Binding to the receptor, it prevents signalling across the membrane resulting in blockade of cell growth, proliferation and metastasis.

DOCETAXEL:

It binds to beta-tubulin and enhances its polymerization.

Microtubules are stabilized and their depolymerization is prevented. This results in inhibition of normal dynamic reorganization of the microtubule network that is essential for interphase and mitotic functions.

FLUOROURACIL (5-FU):

It is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate which forms a covalent ternary complex with methyl-THFA and thymidylate synthase (TS) resulting in irreversible inhibition of TS.

It is rapidly metabolized by DPD resulting in plasma $t^{1/2}$ of 15-20 minutes after i.v infusion.[15]

In general, there are 3 main approaches to the initial treatment of locally advanced disease: (1) concurrent platinum-based chemoradiation, with surgery reserved for residual disease;

(2) surgery with neck dissection and reconstruction, followed by adjuvant radiation or chemoradiation, depending on the presence of adverse risk factors; or

(3) induction chemotherapy followed by definitive chemoradiation or surgery.

Approximately 60% of patients with HNSCC present at a locally advanced stage, in which combined modality therapy with curative intent is recommended. Data shows that radiation therapy combined with simultaneous 5-fluorouracil (5-FU), cisplatin, carboplatin as single or combinations therapy of 5-FU with other drugs results

in a increasing survival rate irrespective the radiation regimen. Cetuximab in combination with platinum or 5- FU has emerged as a new alternative regimen for patients who are not treated based on results from the first line treatment. The data from a phase III trial support the role of cetuximab plus radiotherapy as an effective treatment option for patients with advanced HNSCC. Moreover, cetuximab plus radiotherapy led to significant improvements in locoregional control and these survival improvements may be maintained over a long time, with a nine-percentage point advantage for cetuximab plus radiotherapy in the 5-year overall survival rate, compared with radiotherapy alone[16].

CONCLUSION:

Head and neck squamous cell carcinoma is a severe type of cancer where the survival rates are very less. Improper or negligence in treatment may lead to fall in lifespan very rapidly. The main culprits of head and neck cancers are tobacco and excess alcohol intake but, in some cases, genetic factors and human papilloma virus. Preventive measures are much more helpful than treating it, which include remission of tobacco and alcohol intake. Early diagnosis is would be beneficial in increasing lifespan of the patients. Treating with combination therapy is more followed when compared to monotherapy.

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CONFLICT OF INTEREST:

There was no conflict of interest.

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