WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 1, 500-508 Review Article ISSN 2278 – 4357

AN OVERVIEW OF ORAL CANCERS AND ITS CHEMOTHERAPY MANAGEMENT

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Article Received on
28 Oct. 2018,

Revised on 17 Nov. 2018,
Accepted on 07 Dec. 2018

DOI: 10.20959/wjpps20191-12905

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ABSTRACT

Oral cancers are increasing in incidence worldwide. Many new drugs have been approved for their treatment. Paclitaxel and Carboplatin regimen is commonly prescribed and also the safest chemotherapy treatment. This review aim to throw light on the various chemotherapy drugs for the management of oral cancers.

KEYWORDS: Oral cancers, Risk factors, Chemotherapy drugs.

INTRODUCTION

The term oral cancer includes malignancies such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), verrucous carcinoma, nasopharyngeal carcinoma (NPC), malignant melanoma, ameloblastoma and mucoepidermoid carcinoma. Squamous cell carcinoma originating from buccal mucosa, tongue and lips forms the striking majority of malignancies among these.[1-3]

Oral cancer ranks among the top 10 in incidence of cancers in the world. Despite the progress in research and treatment, there is no improvement in the survival in the last years, representing a continuing challenge for biomedical science. This paper aimed to present key aspects of oral cancer, including clinical, histological and molecular concepts for a better understanding of their biological pathways.[4]

Epidemiology

Nearly 12.7 million new cancer cases and 7.6 million cancer deaths occurred in 2008 worldwide.[5] According to GLOBOCAN 2008 released by International Agency for Research on Cancer (IARC), oral cancers form the 3rd most common group of malignancies in India. It is the 2nd most common group of malignancies in males while in females it ranks 4th.[5]

Risk Factors

Oral cancer is a preventable disease and major associated risk factors are smoking and alcohol- present in 90% of cases.[6] In addition combination of both these risk factors further have a synergic effect.[7]

Tobacco

The risk for developing oral cancer is three times higher in smokers compared with nonsmokers.[8] Even the environment with cigarette smoke is risky; as the risk for oral cancer is 87% higher in those who never smoked, but were exposed to an environment with cigarette smoke (involuntary smoking) compared with those who never smoked and not have been exposed.[9]

Cigarette smoke contains several elements that promote cancer and they basically can be grouped into three distinct groups: nitrosamines, benzopyrenes and aromatic amines. These chemicals are called pre-carcinogens.[10] Snuff consumption exposes the oral epithelium to free radicals of oxygen and nitrogen that can affect antioxidant defense mechanisms. Elevated levels of these free radicals are found in oral pre malignant lesions and cancer.[11]

Alcohol

Alcohol can act as a both locally as well as systemically risk factor causing increased permeability of oral mucosa, dissolving lipids components of the epithelium, causing epithelial atrophy and interference in DNA synthesis and repair. Chronic use of it is associated with an impairment of innate and acquired immunity, resulting in increased susceptibility to infections and neoplasms.[12]

Other factors

The other risk factors, are human papilloma virus which is mainly associated with carcinoma of the oropharynx[13] and ultraviolet radiation. The most-common sites of HPV- related head

and neck squamous cell carcinoma (HNSCC) are the tonsils and base of tongue within the oropharynx, with a prevalence rate of 75%.[4]

Management

The treatment of oral cancers include surgery, radiation therapy (external beam radiotherapy and/or brachytherapy), and Coadjuvant therapy (chemotherapy with agents such as cisplatin, carboplatin, 5-fluorouracil, paclitaxel and docetaxel).[14,15] Though the oral cancer is typically treated by one or a combination of these alternatives, however the choice of one or the other depends on the location, size and stage of the primary tumor, comorbidities presented by the patient, nutritional status, its ability to tolerate treatment.[16]

Role of Chemotherapy

In the early 1990s, the focus of treatment in oral cancer was shifted to administering chemotherapy concomitantly with radiation, to take advantage of the radiation enhancing properties of cytotoxics active in Head and Neck Squamous Cell Carcinoma (HNSCC).[17] In the management of potentially curable HNSCC, chemotherapy has been used as Induction Chemotherapy (IC) with several cycles of a drug combination followed by definitive radiation/surgery, as CRT (concurrent chemoradiation) in patients with resectable disease, as CRT for patients with unresectable disease, as IC alternating with radiation therapy and as adjuvant CRT in patients whose resected tumors have high-risk pathologic features.[17]

Several cytotoxic agents that are being used for oral cancers includes Methotrexate, Platinum analogues, 5-FU, Taxanes and Ifofosfamide.[18] To date US FDA has approved six agents for the treatment of HNSCC including five conventional chemotherapy drugs (cisplatin, methotrexate, 5-flurouracil [5-FU], bleomycin and docetaxel) and one targeted agent (cetuximab).[18]

Platinums, including cisplatin and carboplatin are the most commonly used chemotherapeutic agents for oral cancer treatment with responses in 13 – 40% of cases. They belong to the alkylating class of drugs that exert their effects by forming covalent bonds with DNA.

Taxanes act by inhibiting microtubule disassembly, cell cycle arrest and apoptosis in the G2/ M phase of the cell cycle. Docetaxel is a second-generation taxane that displays potent and broad antineoplastic properties.[19]

The combination of cisplatin and 5-FU (PF regimen) is widely used for treatment of oral cancers.[20] However, a series of clinical trials and meta-analyses have suggested that docetaxel plus the standard PF regimen (the TPF regimen) given as induction CT may improve outcomes with acceptable toxicity rates in locoregionally advanced head and neck squamous cell carcinoma compared with PF regimen.[21, 22]

Targeted therapies have been developed to exploit unique tumor factors with the hope of improving efficacy and reducing toxicity. Cetuximab, an epidermal growth factor receptor (EGFR) monoclonal antibody, is currently the only FDA-approved EGFR targeting strategy for oral cancers. It is approved in three specific applications: in combination with radiation for locally advanced disease, as a single agent for recurrent / metastatic disease after failure of platinum-based chemotherapy and in combination with platinum-based chemotherapy plus 5-fluorouracil for the first-line recurrent/metastatic oral cancers.[23,24]

Monoclonal Antibodies (mAbs)

a) Zalutumumab is a high-affinity human IgG1 anti-EGFR mAb, especially effective at inducing antibody dependent cellular cytotoxicity (ADCC). Being completely human-derived, it is predicted to have a low immunogenicity profile compared with cetuximab, thus minimizing the risk of hypersensitivity reactions and compromising treatment efficacy in prolonged use. A Phase III trial to determine whether zalutumumab as a component of primary curative RT or CRT increases locoregional control in oral cancer patients is ongoing.[25]

b) Panitumumab is a human IgG2 anti-EGFR mAb, which may not elicit ADCC as strongly as cetuximab, reducing the incidence of life-threatening hypersensitivity reactions.[26]

c) Nimotuzumab is another humanized anti-EGFR mAb with a lower incidence of skin toxicity compared with cetuximab or panitumumab. In contrast to other anti-EGFR antibodies, the intrinsic properties of nimotuzumab requires bivalent binding for stable attachment to cellular surface, thus selectively binding to cells with moderate-to-high EGFR expression. Nimotuzumab is approved for HNSCC in several countries outside the USA.[27]

d) Duligotuzumab – It is a a human IgG1 anti-EGFR/HER3 mAb. A dual targeting anti-EGFR mAb simultaneously blocks two receptors and it is being studied in early phase trials to overcome resistance to cetuximab. While these newer anti-EGFR mAbs are being investigated in an attempt to improve outcomes or reduce toxicity in HNSCC, no preclinical or clinical evidence to date demonstrates superiority with respect to cetuximab.[28, 29]

Tyrosine Kinase Inhibitors

Tyrosine Kinase inhibitors (TKIs) the tyrosine kinase domain of epidermal growth factor receptors (EGFRs) and to inhibit downstream signaling, eventually blocking the proliferation of tumor cells.

a) Reversible EGFR TKIs

Gefitinib is an oral small-molecule reversible EGFR TKI, and was the first TKI to reach Phase III investigation in HNSCC. However because of recent negative study results in clinical trials, it is unlikely to be further developed.[30]

b) Dual and pan-HER TKIs

Lapatinib is an oral reversible dual EGFR and HER2 TKI. Afatinib is another TKI that irreversibly inhibits EGFR (including EGFR vIII), HER2 and HER4 kinases. Afatinib is now under development in several Phase III clinical trials investigating a comparison of afatinib with methotrexate as second-line treatment after failure of platinum-based CT in recurrent / metastatic oral cancers.[31] A new generation of TKIs, the irreversible small molecule pan-HER inhibitors, including Afatinib and Dacomitinib, have been developed. By covalently binding and irreversibly blocking multiple ErbB family kinases, sustained suppression of tumor growth may occur.[32]

Table 1: Summary of the various chemotherapy agents for oral cancers.

Group	Mechanism of Action	Adverse effect
1) Platinum's	All alkylating agents act on both resting as well as dividing cells. These drugs alkylate nucleophilic groups on DNA bases (N7 of guanine is most susceptible) and may lead to cross-linking of bases, abnormal base-pairing and DNA strand breakage.	Gastrointestinal distress, bone marrow suppression, alopecia, secondary leukemias and sterility are common adverse effects of all the alkylating agents.
2) Taxanes	They use platinum instead of alkyl group to form dimers of DNA. is	Nausea and vomiting (maximum among all anti-cancer drugs). These drugs are mild bone marrow suppressants and are nephrotoxic, ototoxic as well as neurotoxic. Cisplatin is most nephrotoxic whereas carboplatin is more hematotoxic (bone marrow suppressant). Carboplatin has less nephrotoxic, ototoxic and neurotoxic potential than cisplatin. Oxaliplatin: dose

		limiting toxicity is neurotoxicity (peripheral neuropathy).
3) Monoclonal Antibodies	It is a monoclonal antibody against EGFR. It is approved for head and neck cancer [with radiation therapy].	Its main adverse effects are skin rash, hypomagnesemia and hypersensitivity reactions.

Table 2: Recent Advances in the Treatment of Oral Cancers.

Therapies	Mechanisms	Drugs
Gene Therapy	High incidence of TP53 mutation (69.8%) and the protein p53 plays an important role in cell cycle and in apoptosis, gene therapy approaches delivering p53 have been tested in oral cancers by direct injection of an adenoviral vector expressing wild-type p53 gene.	1) Gendicine (Adp53- based gene therapy) - First approved by State FDA of the People's Republic of China for the treatment of oral cancers.[33,34]
Immunotherapy	Oral cancer patients often present with a suppressed immune system, featuring dysregulation of immune competent cells and cytokines.	1) Anti-programmed cell death -1 antibody. 2) Multi-cytokine immunotherapy regimen. (IRX-2) 3) Peptide based vaccine, a DNA vaccine.[35]

CONCLUSION

Ultimately, judicious selection of preclinical models will help to define predictive biomarkers and guide emerging therapies for the treatment of oral cancers, with many new anticancer drugs emerging for the treatment of oral cancers.

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