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REVIEW ARTICLE

NEW MODALITY OF CHEMOPREVENTION FOR HNSCC– A REVIEW

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ABSTRACT

Oral cancer is one of the 6th most common cancer in the world. It causes considerable morbidity with a 5 year survival rate of 40-60%. The development of an effective chemoprevention agent for head and neck squamous cell carcinoma (HNSCC) has made limited progress over the past three decades. Many micronutrients have been tried as a chemopreventive agents like vitamin A, E, curcumin and dietary agents. Due to the disappointing outcomes of those agents the molecular agents have come into play. Hence, in this review, we summarize the biological basis of HNSCC chemoprevention i.e., molecular target interventions by COX-2 and EGFR inhibition. Finally we introduce the concept of green chemoprevention, interventions based upon whole plant foods or simple extracts that may become cost effective option for the next generation of studies.

INTRODUCTION

In Indian scenario annually 1,30,000 people succumb to oral cancer, which translates into approximately 14 deaths per hour. The reason for high prevalence of oral cancer in India is primarily because of tobacco which is consumed in the form of gutka, quid, snuff or misri (Sridharan, 2014).[1]70% of the population has been affected by oral squamous cell carcinoma (Meyers *et al*., 2009). Head and neck squamous cell carcinomas (HNSCC) are a public health problem world-wide. Despite the advances of curability of early stage disease with surgery/ radiotherapy, most of the patients present with advanced disease. Survival of advanced HNSCC has improved little in the last two decades combined with newer modality approaches. Therefore interfering with the early carcinogenic process before the establishment of invasive cancer would be a promising approach to reduce the incidence and mortality of the disease (Harrison *et al*., 2009). To control head and neck cancers and many deadly epithelial cancers, great efforts are being made to develop effective new strategies. One promising approach was found to be chemoprevention.

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Chemoprevention is the use of drugs/agents to halt or reverse carcinogenesis through regulation of growth and differentiation. Studies regarding cancer chemoprevention in head and neck have been directed at the reversal of premalignant lesions and the prevention of second primary tumors (Harrison *et al*., 2009).Thebiologic basis of HNSCC chemoprevention is multistep carcinogenesis and field cancerization (Sheth *et al*., 2015). There are various levels of prevention which include primary, secondary and tertiary. Primary prevention address towards the root cause of cancer, mainly aimed towards prevention at grass root level. Secondary prevention aims towards early recognition and treatment by early diagnosis and intervention. Tertiary prevention focuses on the prevention of second primary tumors. Chemoprevention falls under secondary prevention. Several micronutrient agents like vitamin A, retinoids, beta carotene, curcumin and vitamin E have been tried as chemopreventiveagents (Chapprawal *et al*., 2012).The disappointing clinical outcomes of micronutrient interventions for chemoprevention mainly due to substantial toxicity and poor long-term efficacy, had turned interest toward molecular targets (Sheth *et al*., 2015). This review paper discusses role of various newer molecular agents in HNSCC like COX-2 inhibitors, EGFR and green chemo preventive agents. Epidermal growth factor receptor is a transmembrane glycosylated phosphoprotein with tyrosine kinase activity. It

mediates signal transduction for epidermal growth factor and transforming growth factor alpha which are the most important pathways for the development of cancer till date. It also regulates cell growth in cell lines in various tumours, where its over expression in transfected cells results in transforming potential. EGFR seemed to be increased with larger tumor size, advanced stage and worse prognosis. Expression of TGF alpha and EGFR in primary tumors are associated with decreased disease free survival, independent of cervical lymph node metastasis there by suggesting the biological importance of this autocrine pathway in HNSCC progression (Harrison *et al*., 2009). A study by Lo *et al.* in 37 cases of oral squamous cell carcinoma for nuclear EGFR using standard IHC methods found that 24% of cases had nuclear EGFR in more than 5% oftumor cells. (rebeiro *et al*). (Harrison *et al*., 2009). A phase Ib study evaluated the combination of celecoxib 400 mg twice daily and escalating doses of erlotinib in patients with OPLs. In 4 to 7 patients there was histological response observed. Tolerability was affected by dose-related erlotinib toxicities. Regard to the maximum tolerated dose of erlotinib it was 50 mg daily, only one-third of the FDA-approved dose for treating lung cancer (Wang, 2005).

COX enzyme inhibitors, such as NSAIDs, have been used as anti-inflammatory, analgesic, and antipyretic agents in conditions like rheumatoid arthritis and many other diseases for many years, but it was discovered recently that they could be used to prevent or treat cancers. In comparision with traditional COX inhibitors, COX2 inhibitors are relatively newer agents. There is an up regulation of COX-2 seen especially in DNA aneuploid of oral premalignant lesions and also in oral carcinogenesis. This enzyme is not expressed in normal mucosa but it is expressed to some extent in dysplastic oral mucosa and in most of the oral carcinoma specimens. Treatment with NSAID's, induces a significant dose- and time-dependent cell growth reduction followed by an increase in apoptosis. The precise mechanism by which these inhibitors affect carcinogenesis development is not clear, it is believed that COX inhibitors can affect multiple mechanisms that are important in carcinogenesis. They include inhibition of apoptosis, stimulation of angiogenesis (VEGF), immune suppression, enhanced invasiveness and increased mutagenesis. Selective COX-2 inhibitors specifically target COX-2 but not COX-1 and so, produce much lower toxicity than traditional NSAIDs had permitted the investigation of systemic COX-2 targeting (Saba, 2014).

Oral ketorolac rinse, was studied in a double-blinded Phase IIb study in patients with OPLs which showed that topical administration of ketorolac was safe and associated with a 30% clinical response rate, and a similar rate of spontaneous regression was observed in the placebo group (Mulshine, 2004). Patients with OPLs were assigned to celecoxib 100 mg twice daily, celecoxib 200 mg twice daily, or placebo for 12 weeks. Pre and post-treatment measurements showed no significant difference in response rates in relation to clinical and histologic changes. A high rate of spontaneous regression (33%) was observed in placebo-treated patients (Wang, 2005). The global epidemiologic studies highlighting the reduction in cancer risk have been associated with diets rich in fruits and vegetables which had given rise to the concept of ''green chemoprevention.''

Many plants are rich in phytochemicals, which are non-nutritive constituents possessing anticarcinogenic and antimutagenic properties. Phytochemicals are chemical compounds that occur naturally in plants (phyto means "plant" in greek). Some are responsible for color and other have organoleptic properties. Some examples include Brassicates (broccoli, soybeans, brussels sprouts, cabbage), green tea, soyabeans, spinach etc. Many Epidemiologic studies have highlighted the protective effect of Green tea and its associated polyphenols against epithelial malignancies. Tea contains certain compounds like catechin, epigallocatechin 3-gallate (EGCG), that has numerous biological effects not only limited to antioxidant property but also to prevent second primary tumors. It mainly acts by 3 mechanisms i.e., by Inhibhiting intracellular oncoprotein signaling along the PKC/RAS/MAPK or P13-kinase/AKT pathways, Inhibhiting pro proliferative, anti-apoptotic transcription factors, NF-Kb and AP-1 and enhancing carcinogen detoxifying enzymes and DNA repair proteins (Sheth *et al*., 2015).

A study done in china using green tea (3g mixed tea oral capsule plus topical) showed 30% reduction in size of the lesion.[9] In a prospective cohort study of 8552 Japanese adults, there found to be a decreased risk and delayed onset of cancers in individuals who drank more than 10cups of green tea daily when compared to those who drank less than 3 cups per day.[10] Interventions based on whole plants when compared to pharmaceutical agents ease the production, distribution and sustainability of chemoprevention – especially poorly resourced countries (Sheth *et al*., 2015).

Conclusion

Despite the inherent challenges, the future of chemoprevention remains promising in HNSCC. Multiple subsequent clinical trials testing molecular targeting agents and phytochemical approaches have been tried preclinically, but have failed to make clinical path. Hence various clinical trials are required to bring an effective clinical change for prevention of HNSCC. In developing countries, the identification of a cost effective, well-tolerated, affordable, plant-based intervention to prevent HNSCC would have a major global impact on mortality and quality of life in patients at risk.

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