Review Article

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Nutraceuticals as Chemopreventive Agents for Oral Squamous Cell Carcinoma: Hype or Hope?

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a global health problem and a leading cause of morbidity and mortality**.** Consumption of Tobacco products, smoking and alcohol are the predominant risk factors, although other factors such as diet (malnutrition) may affect the risk. Toxic agents and free radicals released from these agents cause oxidative damage to cells of the oral tissue. Data from previous studies suggested, Nutritional agents (such as carotenoids, curcumin, flavonoids) with their antioxidant and anti-inflammatory properties have a significant role in modulating genetic pathways associated with carcinogenesis. Evidence from several animal and clinical studies on oral potentially malignant disorders showed an inverse relation between levels of antioxidants and risk of progression to cancer. Expanding knowledge on cancer genomics made it possible to develop strategies that target specific dysregulated molecular events associated with the pathogenesis of cancer. Prevention using natural chemopreventive agents (Nutraceuticals) has been suggested as an innovative strategy. Studies had shown treatment with nutritional agents has the potential to hamper or reverse steps involved in carcinogenesis.

Keywords: Oral cancer, chemoprevention, Nutraceuticals.

INTRODUCTION

Cancer of oral cavity is one of the most common malignancies leading to death worldwide. It ranks 12th among all cancers.[1]Majority of oral cancers are squamous cell carcinomas.[2]Oral squamous cell carcinoma (OSCC) survival rate has not dramatically improved despite remarkable advances in treatment protocols (surgery, radiotherapy, and chemotherapy). This can be partly explained by genetic predisposition, which is a major event in oral cancer pathogenesis because most of the tumors develop in preneoplastic fields of genetically altered cells.[3]Refinement in surgical resection, reconstructive techniques, and advances in radiotherapy planning, delivery techniques such as Intensity Modulated Radiation Therapy(IMRT), Image Guided Radiotherapy(IGRT) yielded favorable outcome for patients with early stage disease. But, in locoregionally advanced OSCC, surgical excision removes only grossly evident disease. It does not address the spread of clonally related cells into normal appearing mucosa. In this case, even multimodality treatment (surgery in combination with radiotherapy and /chemotherapy) fails to prevent life threatening recurrence and second primary tumors. Overall prognosis in such cases remains to be poor

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regarding disease control and preservation of organ function. These failures highlight the inadequacy of current treatment protocols.

Therefore, efforts have been made to find alternative modalities of treatment which results in the more favorable clinical outcome and decrease morbidity among the patients. Current research on high-risk population suggests that chemoprevention is a rationale and appealing strategy. The present paper summarizes the current literature on chemopreventive ability and therapeutic potential of dietary agents in the treatment of oral cancer.

Chemoprevention:

Sporn in 1976 defined Cancer chemoprevention as 'the natural, synthetic or biological, chemical agents that can be used to reverse, suppress or prevent carcinogenic progression.[4] The two important concepts "Multistep carcinogenesis" and "field cancerization" form the biologic basis of chemoprevention. The field cancerization model proposed by slaughter and colleagues in 1953 hypothesized that exposure of the entire oral mucosa to carcinogens predispose mucosa to develop cancer at multiple sites within the oral cavity. Recently genetic analysis showed that tumors developing at distant sites within the oral cavity often are derived from the same initial clone. This multifocality of the oral carcinogenesis process makes it difficult to interrupt the progression to cancer through the surgical excision of potentially malignant lesions. According to multistep carcinogenesis, epithelial carcinogenesis of head & neck cancers progress through distinct stages and results in cancer.[5] Chemopreventive trials aim to hinder, reverse or inhibit this biological mechanism involved in carcinogenesis. The target of chemoprevention in oral squamous cell carcinoma is to reverse potentially malignant lesions and prevent the occurrence of second primary tumors.

The presence of clinically detectable potentially malignant lesions such as leukoplakia, erythroplakia, identifiable risk factors (e.g. tobacco) and well characterized patterns of relapse make OSCC cases ideal models for testing relative efficacy of novel modalities.

Natural agents for chemoprevention:

Human body possess an inherent antioxidant mechanism to scavenger and counteract damage by the free radicals. Deficiency of these antioxidants occurs because of improper diet. Also, insufficiency of antioxidants occurs due to excessive consumption of tobacco products leading to an imbalance. This can result in oxidative damage to DNA, structural alterations in proteins and lipids. Oxidative stress created is involved in the initiation, promotion, and progression of cancer. Evidence from previous studies suggested that treatment with nutritional agents (rich in antioxidants) counters this oxidative damage and may prevent or inhibit one or more steps involved in carcinogenesis.

Local recurrence and second primary tumors after treatment (surgery alone or in combination with radiotherapy/chemotherapy) pose a major dilemma in the management of locally advanced OSCC. In most of the cases, curative treatment is suboptimal. Many investigators opined that standard treatment complemented with biologically active and targeted therapies would significantly improve prognosis. More emphasis was laid on developing preventive strategies in recent years. These Chemopreventive agents are suggested to use for a longer period for optimal clinical results. These natural agents do not cause dose related toxicity when used for a prolonged period.

The term "NUTRACEUTICAL," a combination of the words ''nutrition'' and "pharmaceutical" was coined by Dr. Stephen De Felice.[6] He defined it as "foods, food ingredients or dietary supplements that demonstrate specific health or medical benefits including the prevention and treatment of disease beyond basic nutritional functions."[7]In the past, usage of nutraceuticals was limited to achieve recommended daily requirement of the body for health. Expansion of knowledge and various animal studies on nutraceuticals widened the horizons. Currently, they are increasingly used in the treatment of major morbidities like cardiovascular disease and cancer.

Nutraceuticals are found as natural products from

- Food industry

- Dietary supplements like cereals, soups, beverages
- Pharmaceutical industry
- Newly emerged bioengineered microorganisms, agro products or active biomolecules.[8]

Nutraceuticals being used so far in clinical trials for OSCC:

Vitamin A and its derivatives such as retinoids and carotenoids, Vitamin E, Curcumin, Flavonoids, Green tea, Folates, Selenium

Vitamin A and its derivatives:

Carotenoids (Pro Vitamin A): Carotenoids represent a diverse group of natural pigments of polyene type (beta-carotene, lycopene, beta cryptoxanthin etc.,).[9] They are capable of metabolic conversion to vitamin A in the body of higher animals. Carotenoids modulate cellular differentiation and proliferation. Anticarcinogenic effect is due to its antioxidant activity, ability to counteract damage by free radicals, role in inhibition of lipid peroxidation.[10]Beta carotene is the primary source of vitamin A in the diet. A systematic review and meta-analysis on dietary carotenoid intake demonstrated that high levels of carotenoid intake might protect against the risk of head and neck cancer. [11]

Lycopene: It is a fat-soluble carotenoid. It is natural constituent of red coloured fruits and vegetables (peach, apricot, watermelon, papaya, etc.) Tomatoes are the rich source of lycopene. Lycopene does not have provitamin A activity and most of its chemical properties are different from other carotenoids. It is a potent antioxidant, inhibits proliferation of cancer cells, regulates transcription, inhibits cell cycle progression. Lycopene is being widely used for the treatment of oral potentially malignant disorders such as oral leukoplakia, lichen planus, oral submucous fibrosis. There were no reported adverse effects even at high intake levels up to 3g/kg/day of dietary or formulated lycopene.[12] Singh et al. evaluated efficacy of lycopene in the management of oral leukoplakia. They randomly divided patients into three groups (Group A - 8mg lycopene/day, Group B - 4mg lycopene/day, Group C - placebo). The results showed that patients in Groups A, B, and C had mean clinical responses of 80%, 66.25%, and 12.5%, respectively.[13]The positive results suggest lycopene can be used in the management of premalignant lesions. Antineoplastic ability of lycopene was confirmed by Cell culture studies, where lycopene inhibited the KB1 tumor cell proliferation and significantly decreased proliferation nuclear cell antigen (PNCA).[14,15]Although preclinical research established antineoplastic potential of lycopene, there are very limited human trials to support association between lycopene and reduced risk of cancer.[16]

Retinoids:

Retinoids regulate cell growth and gene expression through nuclear transduction signal modulation mediated by nuclear Retinoic Acid Receptor (RAR), Retinoid X Receptor (RXR). Studies had shown inhibition of one of these receptors in early stages of head and neck squamous cell carcinoma and potentially malignant disorders of oral cavity.[17]

All-trans-retinoic acid is physiologically active form of vitamin A. It has two isomers, 9 cis retinoic acid (9cRA) and 13 cis retinoic acid (13cRA). These two isomers had been widely used in clinical studies. Hong et.al. (1986) demonstrated chemopreventive ability of 13cRA(isotretinoin) in a trial that included 44 oral leukoplakia patients randomized to receive high-dose isotretinoin at the dose of 1 to 2 mg/kg/day or placebo for 3 months. They observed a remarkable decrease in the size of lesion in study group compared to controls.[18] However, relapse occurred in few patients suggesting need for extended duration of treatment. Activation of multiple signaling pathways by retinoids caused substantial toxicity along with beneficial effects. These were reversed after cessation of therapy. In another randomized, placebo-controlled chemoprevention trial by Honget al. (1990) performed in 103 patients diagnosed with Head and Neck SCC(larynx, pharynx, or oral cavity) usinghigh-dose 13-cRA (50 to 100 mg/m^2/day for one year), there was no improvement in overall survival rate.[19]

Bolla et al. evaluated the efficacy of second generation retinoid, etretinate in 324 patients

diagnosed with early-stage squamous cell cancers of the oral cavity or oropharynx. They reported neither there is a difference in five-year survival rate nor in the occurrence of second primary tumors. Also, there was higher incidence of labial, cutaneous, ocular toxicities on etretinate arm.[20]

Papadimitrakopoulou et al. conducted a nonrandomized clinical trial in 36 patients with advanced premalignant lesions using IFN- alpha, alpha tocopherol, and 13cRA for one year. This trial showed decrease in incidence of laryngeal lesions but had no effect on oral lesions.[21]

Vitamin E:

Alpha-tocopherol is naturally occurring form of vitamin E which is physiologically active in humans. It is a potent antioxidant. Animal studies reported systemic alpha-tocopherol has an inhibitory effect on tumor formation.[22,23] Combination therapy with alpha tocopherol and beta carotene caused regression of experimental SCC in hamster buccal mucosa.[24]Benner et al. performed a nonrandomized Phase II trial using alpha-tocopherol in oral leukoplakia patients. Twenty patients (47%) had a clinical response, with nine (21%) showing histologic effect.[25]

Vitamin C (Ascorbic acid):

Vitamin C is a potent antioxidant. It defends the body from damage caused by harmful reactive oxygen species. Cameron et al. first reported beneficial effects of high dose of Vitamin C in terminal stage cancer.[26]At low concentrations ascorbic acid act as antioxidant and at high concentrations it induces apoptosis of tumor cells.[27]Furthermore, recent studies on the pharmacokinetics of vitamin C showed IV is the preferred route of administration to attain optimal plasma levels of drug compared to oral route. Even high doses of oral administration will increase plasma concentration from 70 μmol/L to a maximum of 220 μmol/Whereas IV administration can raise plasma concentrations to a maximum of 14000 μmol/L. In vitro studies showed concentrations as high as 1000–5000 μmol/L are selectively cytotoxic to tumor cells.[28]A systematic review by Jacobs et al. (2015) concluded that ascorbate supplementation in cancer patients neither enhanced antitumor effects of therapy nor reduced toxicity.[29]Although, vitamin c has been proved to be a potent antioxidant, there is controversy regarding its role in cancer prevention and treatment. Further research is required to unravel chemopreventive ability of vitamin C

Curcumin:

Curcumin is a polyphenol derived from Curcuma longa. Usage of curcumin as healing agent dates back nearly 4000 years. Earlier investigators found the correlation between widespread use of dietary curcumin and low incidence of gastrointestinal cancers.[30]Phase 1 studies conducted on the chemopreventive ability of curcumin by chenget al. (2001) claimed curcumin is safe and tolerable even in high doses (8g/day).[31]Antineoplastic activity of curcumin is attributed to its modulatory effect on components of the tumor microenvironment. NF-kB is an inflammatory cytokine activated by various carcinogens. Activated NF-kB may cause cellular transformation, tumor promotion, angiogenesis, tumor invasion and metastasis. Curcumin downregulates tobacco induced NF-kB and COX-2 expression in oral premalignant and malignant cells.[32] However, major limitation to curcumin is its low systemic bioavailability because of its rapid metabolism. Novel strategies to improve bioavailability are being developed such as liposomal curcumin formulations, encapsulation in polymeric nanoparticles.[33]

Flavonoids:

Flavonoids encompass a large group of low molecular weight polyphenolic compounds of plant origin present in foods and beverages. Chemopreventive ability is attributed to their antioxidant, antimutagenic and antiproliferative property.[34] Case control studies showed an inverse relation between consumption of flavonoids and risk of cancer.[35,36] A pooled data analysis from 22 case-control studies (14,520 cases and 22,737 controls) by INHANCE (International Head and Neck Cancer Epidemiology) in 2011 stated that high fruit and vegetable intake was associated with reduced risk of cancer. Tea catechins are one of the most commonly investigated flavonoids in clinical trials on OSCC.[37]

Green tea:

Green tea is derived from Camellia Sinensis. It is rich in polyphenols such as catechin, epigallocatechin -3-galleate (EGCG). Many epidemiological studies showed antioxidants in green tea are associated with antitumor properties.[38] Invitro studies showed EGCG suppressed beta catenin signaling and cyclin D1 expression. It also caused cell arrest at G1 phase. Li N et al.[39] conducted a double blinded intervention trial using 760 mg of mixed tea capsules q.i.d. and 10% mixed tea ointment topically for 6 months in oral leukoplakia patients. They found a decrease in the incidence of micronuclei in the treated group compared to controls. Pathological examination using silver-stained Nucleolar Organizer Regions (AgNOR) and the proliferating index of Proliferation Cell Nuclear Antigen (PCNA) in oral mucosa cells showed decreased cell proliferation in the treated patients. Most of the clinical trials EGCG was used for prevention of cancer. Administration of a green tea extract (2000–2500 mg/day) to smokers for four weeks reduced DNA damage in oral keratinocytes and reduced cell growth.[40]

Folate: It is a water-soluble vitamin. It is found naturally in green leafy vegetables, legumes, cereals. Folic acid is the synthetic analog of folate. Folate plays a vital role in nucleic acid synthesis by mediating transfer of one- carbon units. There is a paucity of literature regarding the chemopreventive potential of folate. Most of the studies showed data regarding intake of natural folate. Pooled data analysis by INHANCE (2015) from 10 case control studies found an inverse relation between folate intake and overall oral and pharyngeal cancer risk. Their results also showed highest oral and pharyngeal cancer risk was observed in heavy alcoholics with low folate levels as compared to never/ light drinkers with high folate.[41]

Selenium: Selenium is an essential micronutrient. Anticancer effect of selenium is mainly through selenoproteins, which are involved in cell metabolism. Data from epidemiological studies had shown low levels of SELENBP1(Selenium Binding Protein 1) could be associated with tumor cell proliferation, invasion, metastasis, and resistance to treatment.[42] Chen et al. (2016) noted significant changes in SELENBP1 levels during tumorigenesis. However, no difference was observed during progression. They also claimed low SELENBP1 expression was associated with more chance of tumor recurrence and metastasis.[43]

CONCLUSION

Along with attempts to improve the cure rate of oral cancer, concerted efforts to prevent disease in the community should be undertaken. This applies for high-risk population and high-risk individuals. A targeted prevention in these groups using agents targeted to key molecules in oral carcinogenesis process should have an impact on lowering the disease morbidity and mortality. Expansion in clinical oncology and advances in molecular biology provided insight to define these high-risk individuals, lesions &novel chemopreventive targets. Despite extensive data from preclinical trials regarding the therapeutic potential of nutraceuticals, promising results were not obtained in human trials. The major limitations with most of the nutraceuticals were their low bioavailability and inadequate target delivery techniques.This issue has been partly addressed by "Nano chemoprevention" in which chemopreventive agents were encapsulated with biocompatible nanoparticles. This method significantly increases bioavailability. Studies are ongoing to assess the efficacy of this modality of drug delivery. Also, the current evidence did not elucidate specific therapeutic window of nutraceuticals. Further research is required to validate the routine use of these drugs as a part of standard treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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