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CHEMOPREVENTION OF ORAL CANCER: A PROMISING VENTURE

Shyam Sundar Behura, * Dhirendra Kumar Singh, ** KMK Masthan, *** N. Aravindha Babu, † Sushila Sah ††

* Senior Lecturer, Department of Oral & Maxillofacial Pathology, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India
** Senior Lecturer, Department of Periodontics & Oral Implantology, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India
*** Professor & Head, Department of Oral & Maxillofacial Pathology, Sree Balaji Dental College & Hospital, Chennai, India
† Professor, Department of Oral & Maxillofacial Pathology, Sree Balaji Dental College & Hospital, Chennai, India
†† Intern, Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha, India

ABSTRACT

Oral cancer is the sixth largest group of malignancies worldwide and has known etiologic factors along with some demonstrable potentially malignant disorders. Thus, prevention of oral cancer is easier and convenient than its management. Chemoprevention of oral cancer is an appealing and promising strategy and has been studied extensively. Many clinical trials on the role of retinoids, vitamin A, beta carotene, vitamin E have been conducted. In some cases it has given very promising results whereas in some its effectiveness is questionable especially in terms of toxicity. Polyphenols as chemo-preventive agents have been extensively researched and many of them have given positive results. Recently, role of biomarkers and molecular targeted agents are being studied which includes H-ras gene, Epidermal Growth Factor Receptor (EGFR) inhibitors, p53 gene target compounds, Cyclo-oxygenase-2 (COX-2) inhibitors and NF-κB. This article reviews the various aspects of chemoprevention and the various chemo-preventive agents tried for oral cancer.

KEYWORDS: Chemoprevention; oral cancer; chemo-preventive agents

INTRODUCTION

Human oral cancer is a global threat. Its occurrence is multifactorial with some known etiologic factors. Oral cancer is preventable with 70% of it developing from clinically demonstrable potentially malignant disorders.[1] But still it is one of the most common cancers in the world. Given the high incidence of oral cancer throughout the world, an intervention is definitely needed. To achieve this, the researchers have continually introduced different weapons against it. One of these weapons is the use of natural or synthetic chemicals, to reverse, suppress, or prevent the process of carcinogenesis and popularly known as Chemoprevention. Moreover, preventing oral cancer through diet has attracted much of attention. There are many chemo-preventive agents available and newer agents are frequently discovered and tried. Currently, the National Cancer Institute (NCI) has made chemoprevention research a top priority with more than 400 potential agents currently under investigation. Each of these agents has its own mechanism of action with some or no side-effects. A number of clinical trials has been done using different chemo-preventive agents and have obtained varied results. Some of the chemo-preventive agents tried on oral cancer are: beta-carotene, retinoids, vitamin A, vitamin E, dietary agents like: tomato, turmeric, soybeans, green tea etc. Although it sounds promising, the scenario is little different. There are different school of thoughts regarding the use of chemoprevention in cancers. In some cases it has given very promising results whereas in some its effectiveness is questionable especially in terms of toxicity. This is one of the reasons why newer agents are now being stressed upon for potentially appreciable therapeutic effect. Recently, molecular targeted approach which includes H-ras gene, Epidermal Growth Factor Receptor (EGFR) inhibitors, p53 gene target compounds, Cyclo-oxygenase-2 (COX-2) inhibitors, NF-κB are the centre point of research. Prevention through chemoprevention is an extensively studied strategy and continues to hold promise as a way of diminishing the morbidity and mortality associated with oral cancer.

RATIONALE FOR CHEMOPREVENTION OF ORAL CANCER

The multiplicity of oral carcinogenesis process along with the concept of field cancerization and Secondary Primary Tumors (SPTs) makes it difficult to interrupt the progression of oral cancer through the surgical removal of a potentially malignant disorder. This calls for an urgent need for increased prevention of oral cancer.In view of that, the success of several clinical trials as well as basic research has suggested Chemoprevention as an appealing strategy. Cancer Chemoprevention was first coined by Sporn in 1976 and was defined as the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression.[2] Chemoprevention is a vital component of the secondary preventive stage and its action can be directed towards potentially malignant disorders in order to reduce the morbidity and mortality associated with oral cancer. The potentially malignant disorders are readily accessible to visual examination, diagnostic sampling, and evaluation of response to treatment thus making them an ideal model for trying chemo-preventive strategies. In addition, oral cancer has a well-defined tumor progression model in which cancer progresses from normal epithelium to mild, moderate and severe dysplasia to carcinoma in situ and frank invasive cancer. As a result, chemo-preventive agents can be targeted at various levels other than normal to stop progression of a dysplastic lesion into carcinoma. Moreover, as it is widely accepted that a dysplastic lesion carries a greater risk of malignant transformation than a non-dysplastic one, the lesions can be effectively screened at every stage and biopsy done to study histopathologically before and after the usage of chemo-preventive agents.[3]

RETINOIDS AND VITAMIN A

Retinoids are by far the most studied and active chemo-preventive agents in head and neck cancer. Specific retinoids studied include retinol, retinyl palmitate, ATRA, 13-cis-retinoic acid (13cRA), etretinate, and fenretinide. Retinoid chemoprevention strategies that have focused on head and neck cancer involve either attempts to reverse potentially malignant disorders or to prevent the development of SPTs.[4] Retinoids have been shown to induce apoptosis, decrease growth rate of epithelial cells, suppress process of carcinogenesis and reduce free radicals. In 1986, Hong *et al*., reported the results of their first prospective, randomized, double-blinded clinical trial of high dose 13cRA (1-2 mg/kg per day) in oral leukoplakia which stated that clinical responses occurred in 16 (67%) of the 24 patients in the 13cRA group and in 2 (10%) of 20 patients in the placebo group (P=.002). The histopathologic improvement (reversal of dysplasia) rate also was higher in the retinoid arm (54% versus 10%; P =.01). The major clinical limitations included substantial toxicity and a high rate of relapse (>50% within 2-3 months of discontinuing therapy).[3] Subsequently, Lippman *et al*., investigated a low dose of 13cRA to address the toxicity and relapse problems of the first randomized trial. Patients received a high dose of isotretinoin (1.5 mg/kg per day) for 3 months followed by maintenance therapy (0.5 mg/kg per day) for 9 months versus beta-carotene (30 mg/day) for 9 months. The study showed 92% continued response or stable disease in isotretinoin maintenance versus 45% in beta-carotene (P<.001).[5] In 1988, Chiesa *et al*., evaluated the efficacy of 4-HPR maintenance therapy versus no intervention following complete laser resection of Oral Potentially malignant lesions (OPLs). He reported 8% of patients in the treated group and 29% of patients who received no intervention were found to have local relapses or new lesions.[3] Another study done by Koch using different derivatives of all-trans retinoic acid, over 60 % of selected cases of homogenous leukoplakia showed early positive results. After follow up of 6 years, nearly 45% of cases showed complete or partial remission. The rest showed relapses or even progression.[3] The effect of retinoids on SPT prevention in Stage I or Stage II Head and Neck Squamous Cell Carcinoma (HNSCC) has been studied as a placebo-controlled double-blinded study by khuri et al. who reported an annual SPT rate of 4.7% in both arms with no significant differences in overall survival or recurrence-free survival.[6] Vitamin A is a fat soluble vitamin essential for normal development of epithelium. Various epidemiologic surveys suggest that the risk of oral carcinogenesis is increased with Vitamin A deficiency. Stich *et al*., in his study compared vitamin A (200 000 IU/week orally for 6 months)

with placebo in users of tobacco or betel nut with well-developed leukoplakia. Complete remission rates in the vitamin A and placebo groups were 57.1% and 3%, respectively. The development of new keratosis with atypia was suppressed in 100% of the treated group versus 21% of the placebo group.[3] Different side effects of vitamin A and retinoids in the form of cheilitis, facial erythema, conjunctivitis, hypertriglyceridemia and skin dryness have been reported especially in high doses. It often becomes difficult for the patient to tolerate these effects of systemic treatment and high rates of relapses on discontinuation.

BETA CAROTENE

Beta carotene is one of the most important member of the carotenoid family (Greek 'beta' and Latin 'carota' (carrot)) and is present abundantly in strongly red orange-coloured pigmented plants and fruits. Carrots, tomato, beans are common sources. It is a phytochemical with anti-cancerous and antioxidant properties. It is also much less toxic when compared to Vitamin A.[7] In a phase II study done by Garewal et al.,[8] a high response rate of 71% was seen using beta carotene in leukoplakia. Twenty-four patients were evaluated of which 17 had major responses (2 complete, 15 partial). Another study on the use of beta carotene on oral leukoplakia by Suda *et al*., showed a response rate of 44.4% with no significant toxicity.[3] In a clinical trial of 79 patients with oral leukoplakia, Kaugars *et al*., employed 30 mg/d of beta carotene, 1000 mg/d of ascorbic acid, and 800 IU/d of alpha-tocopherol for 9 months and found clinical improvements in 55.7% of those patients.[9] Although, it looks very much promising but in many studies it has been shown to be less effective than other chemo-preventive agents. Like in a study done by Sankaranarayanan *et al*., they conducted a double blind placebo controlled trial comparing the effectiveness of vitamin A and vitamin B in subjects with oral leukoplakia. Complete regression rates were 10% with placebo arm, 52% with vitamin A and 33% with beta carotene, showing beta carotene to be less effective than vitamin A but well tolerated with insignificant toxicity.[3]

LYCOPENE

Lycopene in tomatoes (Solanum lycopersicum) is also a carotenoid with antioxidant and anticancer properties. Kumar *et al*.,[10] conducted a study to evaluate the efficacy of lycopene in oral submucous fibrosis and suggested that lycopene should be used as a first line of therapy in the initial management of oral submucous fibrosis.

VITAMIN E

Vitamin-E is the collective term for a family of chemical substances that are structurally related to alpha-tocopherol. Alpha-tocopherol, the major constituent of Vitamin E has antitumor proliferation capacity as well as function as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids.[11] Benner *et al*.,[12] in his trial in 1993 showed that among 43 patients with oral leukoplakia who took vitamin E twice daily for 24 weeks had clinical response of 46% and histological response of 21%. The treatment was well tolerated, without any toxicity higher than grade 2 and with good compliance. On the other hand, Miller *et al*.,[13] performed a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized controlled trials. It was found that high doses of vitamin E supplementation (> 400 IU/d) may increase all-cause mortality and should be avoided.

VITAMIN C

It is a water soluble vitamin and also a potent antioxidant. Nagao *et al*.,[14] conducted a randomized controlled trial on treatment of oral leukoplakia with low dose of beta carotene and vitamin C supplements. Vitamin C in the study was neither effective for clinical remission, nor for protection against the development of cancer. This study also didn't support the hypothesis of chemoprevention as an effective treatment for oral leukoplakia which is a potentially malignant disorder.

VITAMIN K

Vitamin K is a group of structurally similar fat-soluble vitamins chemically comprises of phylloquinone (K1), menaquinones (K2), and menadione (K3). Studies have shown that Vitamin K1 arrested cell growth, Vitamin K2 acts on cyclins to inhibit cell cycle and a combination of Vitamin K3 and Vitamin C causes cell death referred to as autoschizis.[15] Still more studies need to prove the efficiency of Vitamin K as a potent chemo-preventive agent.

POLYPHENOLS AS CHEMO-PREVENTIVE AGENTS

Dietary polyphenols as cancer preventives and therapeutic agents is of great interest due to their antioxidant and anti-carcinogenic activities. Polyphenols inhibit carcinogenesis in the stage of initiation, promotion, or progression. They exert protection against oral cancer by inducing cell death and reducing tumor growth, invasion and metastasis.[16]

a) Curcumin

The rhizome of Turmeric (Curcuma longa) contains curcumin, a phytopolyphenolic pigment with anti-inflammatory, antioxidant, antimicrobial, immunomodulatory and antitumor properties. Cheng *et al*.,[17] evaluated the effect of curcumin in patients with oral leukoplakia. In this study, curcumin was taken orally for 3 months. Biopsy of the lesion sites was done immediately before and 3 months after starting curcumin treatment. Histological improvement was seen in two of the seven patients with oral leukoplakia. Moreover, it is has been shown that persistent inflammation has been believed to involve in the multistage of cancer development. As a result, the aberrantly increased activity of nuclear factor kappa B (NF-κB), a key factor in inflammation, is implicated in a variety of human cancers. Curcumin acts as an anti-inflammatory agent through inhibition of NF-κB signaling.[18] Persistent activation of NF-κB has been observed in various cancers including oral cancer. Thus curcumin can be a potential agent in the development of anti-cancer drugs.

b) Green Tea Polyphenols

Epigallocatechin gallate (EGCG), a major polyphenol found in green tea (Camellia sinensis) possesses antioxidant and chemo-preventive properties. Koh *et al*.,[19] in their study administered EGCG to squamous cell carcinoma (SCC) of a syngeneic mouse as an in vivo model (C3H/HeJ mice, SCC VII/SF cell line). Model tumor growth was suppressed and apoptosis was increased suggesting EGCG as a potential therapeutic agent to inhibit hepatocyte growth factor-induced tumor growth and invasion in oral cancer. According to Klass CM and Shin DM, 29 out of 59 patients with oral leukoplakia were randomized to use a mixed tea extract orally as well as a topical tea extract. After the 6-month trial, the oral lesions had decreased in size in almost 40% of the patients treated, which was associated with a decrease in proliferation in the treatment group on histopathologic examination ($P < 0.05$).[20] A recent study in 2014 by Gao F *et al*., reported that EGCG has a profound antitumor effect on human tongue carcinoma cells by directly regulating glycolysis. EGCG dose-dependently inhibited anchorage-independent growth and short-term EGCG exposure substantially decreased EGF-induced EGF receptor (EGFR), Akt and ERK1/2 activation, as well as the down regulation of hexokinase 2 (HK2). HK2, the first rate-limiting enzyme in glycolysis, is considered crucial for tumor initiation and maintenance. HK2 being a new potential target of EGCG, it can be used as a good molecular target for the prevention of human tongue carcinoma.[21] Another recent study by Irimie AL stated that treatment with EGCG activates the expression of the BAD, BAK, FAS, IGF1R, WNT11, and ZEB1 genes and inhibits CASP8, MYC, and TP53 suggesting that EGCG has an excellent potential to become a therapeutic compound for patients with oral cancer, by inducing tumor cell death via apoptosis and autophagy.[22] B-cell translocation gene 2 (BTG2) is an important regulator of cell cycle dynamics in cancer cells. A study published by Lee J *et al*., in 2015, revealed that cell proliferation was attenuated by EGCG via up-regulation of BTG2 expression causing cell cycle G1 phase arrest in oral squamous cell carcinoma cells.[23] Findings from all the studies make EGCG a potent chemo-preventive agent.

c) Black Tea Polyphenols

Black tea contains 8% of catechins, 10% of flavonol glycosides, 12% of theaflavins, and 70% of thearubigens of which theaflavins are considered to be most effective against carcinogenesis. Schuck *et al*.,[24] in his study showed that Theaflavin-3 (TF-3) inhibited more cell growth in HSC-2 cancer cells than normal GN46 fibroblasts. Further studies are required to establish black tea polyphenols as efficient chemo-preventive agent.

d) Resveratrol

Resveratrol, a component of grape skin is one of the well-studied polyphenol with a potential role in HNSCC prevention. Resveratrol induces

significant dose-dependent inhibition of DNA synthesis and suppresses metabolic activation of pro-carcinogens to carcinogens by modulating the metabolic enzymes responsible for their activation.[25]

e) Licorice and its components

Licorice (Glycyrrhiza) is a perennial plant that is cultivated in countries like China, Russia, Spain, Persia, and India. Licochalcone A (LicA) is a major phenolic constituent of licorice exhibiting anti-proliferative and anti-inflammatory properties in human and mouse cells. It exerts inhibitory effects against cancer by inducing apoptosis and cell cycle arrest. LicA decreased the viability of KB human oral cancer cells but had no effect on primary normal human oral keratinocytes. LicA also was reported to inhibit the migration and invasion capabilities of SCC-25 oral cancer cells by suppressing the activity and protein level of MMP-2 and increasing the level of tissue inhibitor of metallopeptidases (TIMP)-2. Decreased expression of phosphorylated p65 (a component of NF-κB) and N-cadherin and increased E-cadherin were also observed in LicA treated SCC-25 cells.[26] Recently, Isoliquiritigenin (ISL), a natural compound extracted from licorice, also has also shown chemopreventive and antitumor activities through cell cycle G2/M phase arrest, apoptosis, and DNA damage.

f) Ellagic Acid

Ellagic acid, a dimer of gallic acid is an antioxidant, anti-proliferative, potent anti-carcinogenic phenolic constituent present in fruits, nuts and vegetables. Presently, ellagic acid is the most potent Casein kinase 2 (CK2) inhibitor, thus making it a potent candidate drug for oral cancer. CK2 is a ubiquitous, essential, and highly pleiotropic protein kinase whose abnormally high constitutive activity is involved in cell growth, proliferation and suppression of apoptosis in neoplasia.[27]

FLAVONOIDS

Deguelin

Deguelin is a derivative of rotenone and classified as rotenoids of the flavonoid family. Deguelin has both anti-proliferation and anti-metastasis activities. However, high-dose deguelin elicits many undesired side effects. A study by Liu YP *et al*., has shown that low-dose deguelin treatment significantly inhibited tumor growth and invasion without systemic toxicity by down-regulating TNF-α-induced NF-κB signalling.[28] The results suggest that it has strong potential for cancer chemoprevention and therapy.

LIGNANS

Honokiol

Honokiol (HK) is a lignan isolated from the bark, seed cones, and leaves of trees belonging to the genus Magnolia. Honokiol has both anti-inflammatory and anti-cancer effect. Cho JH *et al*., in his study[29] suggested that HK inhibited inflammation and induced apoptosis by suppressing both inducible nitric oxide synthase/Nitric oxide (iNOS/NO) and Endoplasmic Reticulum resident protein 44 (ERp44) expression in HN22 and HSC4 cells and xenograft tumors, and thus could be a potent anti-inflammatory and anti-cancer drug candidate for human oral cancer treatment.

ESCULETIN

Studies have shown that Esculetin (6,7-dihydroxycoumarin), a coumarin compound, inhibits proliferation and induces apoptosis in several types of human cancer cells and is regarded as a promising chemotherapeutic agent. A study by Cho JH *et al*.,[30] shows that esculetin had anti-proliferative effect and inhibited cell growth and induced apoptosis by suppressing Sp1 in HN22 and HSC4 cells, suggesting it to be a potent anticancer drug candidate for oral cancer.

LUPEOL

Triterpenes are natural components of human diets. Lupeol is a dietary triterpene found in vegetables such as white cabbage, pepper, cucumber, tomato, in fruits such as olive, fig, mango, strawberry and red grapes. Its chemo-preventive action is attributable to its antioxidant, apoptosis-inducing, anti-inflammatory, anti-proliferative and anti-mutagenic properties.[31]

MOLECULAR TARGETED CHEMO-PREVENTIVE AGENTS

Oral squamous cell carcinoma develops after the accumulation of genetic changes in epithelia exposed to the carcinogens. The multistep carcinogenesis process has open doors for the investigation of biomarkers that may lead to the development of new chemo-preventive agents.

H-ras Gene

GTPase HRas also known as transforming protein p21 is an enzyme that in humans is encoded by the H-ras gene. The H-ras protein is a GTPase is

involved in regulating cell division in response to growth factor stimulation. A mutation in the H-ras gene is found in 27% - 61% of squamous cell carcinoma cases and 30% of oral leukoplakia.[32]

Cyclooxygenase-2 Inhibitors

Cyclooxygenase (COX)-2 is an inducible enzyme produced by many cell types in response to multiple stimuli. Recently, COX-2 over-expression has been found in several types of human cancers including oral cancer.Its overexpression inhibits apoptosis, increases tumor cell proliferation and enhances metastatic potential. These findings provide the rationale for the use of selective inhibitors of COX-2 as chemo-preventive agents. Celecoxib is a highly selective inhibitor of COX-2, with less toxicity and can be used for reversing or stopping oral carcinogenesis at an early stage of disease.[33]

Epidermal Growth Factor Receptor

Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase that is overexpressed in oral dysplasia and invasive cancer and associated with poor prognosis in patients with HNSCC. As EGFR is frequently expressed, use of targeted agents that inhibit EGFR tyrosine kinase can prevent head and neck cancer. Studies on HNSCC cell lines have shown that the combination of EGFR-TKI and celecoxib synergistically inhibited the growth of the HNSCC cell lines with apoptosis in 72% with combined treatment, 21%-50% with single-agent therapy and 8% without treatment.[34]

p53Gene

Mutational inactivation of p53 tumor suppressor is the most frequent event found in most of the human cancers. p53 plays a important role in tumor suppression mainly by inducing growth arrest and apoptosis as well as by blocking angiogenesis. In addition, p53 generally confers the cancer cell sensitivity to chemoradiation, thus making p53 the most appealing target for mechanism-driven anticancer drug discovery. Gene therapy using wild-type p53, delivered by adenovirus vectors, is being studied extensively. Other biologic approaches include the development of oncolytic viruses designed to replicate and kill only p53 defective cells and also the development of siRNA and antisense RNA's that activate p53 by inhibiting the function of the negative regulators Mdm2, MdmX, and HPV E6. p53 based vaccines are now in clinical trial. A number of small molecules that directly or indirectly activate the p53 response are also being tried, of which the most advanced are the p53 mdm2 interaction inhibitors.[35] Further studies are still being done to validate other novel compounds that can target p53 signaling pathways.

CONCLUSION

Chemoprevention is being widely studied and being accepted as a method to kill cancer-prone cells at the early stage of carcinogenesis and preventing the further progress into an invasive carcinoma, thus reducing the morbidity and mortality associated with it. The potentially malignant disorders are readily accessible to visual examination, diagnostic sampling, and evaluation of response to treatment thus making them an ideal model for trying chemo-preventive strategies. Moreover, oral cancer has a well-defined tumor progression model and chemo-preventive agents can be targeted at various levels to stop progression of a dysplastic lesion into carcinoma. In addition to retinoids and beta carotene, polyphenols especially the Epigallocatechin gallate (EGCG) found in green tea shows very promising results. Molecular targeted agents such as H-ras gene, epidermal growth factor receptor (EGFR) inhibitors, p53 gene target compounds and Cyclo-oxygenase-2 (COX-2) inhibitors have high potential to be used as chemo-preventive agents but require further therapeutic validation.Though more trials are required to achieve efficacy and good patient compliance, chemoprevention of oral cancer definitely holds a lot of promise.

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