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REVIEW

Oral cancer chemoprevention: A review

Nanditha Sujir[1], Priyanka G[2], Junaid Ahmed[1*], Anindita Saha[3], Yogesh Chhaparwal[4], Nandita Shenoy[1]

1. Department Oral Medicine and Radiology, Manipal College of Dental Science Mangalore, Manipal Academy of Higher Education, Manipal, India
2. Department Oral Medicine and Radiology, Chettinad Dental College and Research Institute, Tamil Nadu, India
3. Department Oral Medicine and Radiology, Dr. R. Ahmed Dental College and Hospital, West Bengal, India
4. Department Oral Medicine and Radiology, Manipal College of Dental Science, Manipal, Manipal Academy of Higher Education, Manipal, India

Oral cancer is increasing in prevalence and its treatment is associated with high degree of morbidity and mortality. Thus, prevention of oral cancer is of utmost importance. Chemoprevention is the use of natural, synthetic, or biologic compounds to halt, reverse, or prevent the initial phases of carcinogenesis or the progression of neoplastic cells to cancer. This modality has been extensively researched in the last two decades for the prevention of oral cancer with the emergence of new information. Retinoids were the first chemopreventive agents to be tested in clinical settings. Since then, a number of new agents such as COX2 inhibitors, EGFR inhibitors, p53 targeted agents, thiazolidinediones and several natural agents have shown promise in oral cancer prevention. Chemopreventive trials in oral cancer tend to be long term studies and are thus challenging. This review article looks into the clinical evidence for the application of chemopreventive agents in clinical settings and also highlights the recent trends in oral cancer chemopreventive trials.

Keywords: oral cancer, squamous cell carcinoma, chemoprevention

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Introduction

Oral Cancer along with pharyngeal cancer is the 6th most common cancer worldwide [1]. In India, it ranks among the top three types of cancer and accounts for over 30% of all malignancies [2]. More than 90% of oral cancers are squamous cell carcinoma (OSCC) [1]. This entity has been the object of focused research for many years with considerable progress in understanding the pathophysiology, diagnosis and treatment of this disease. However, these advances in research, especially in recent times, have not translated into tantamount improvement in the clinical outcomes. The morbidity and mortality associated with OSCC continues to be high with the overall 5-year survival rate a dismal 50% [3]. This survival statistics is significantly affected by the occurrence of second primary tumors which has a prevalence of about 18% [4] with 5-year survival rates varying between 15% to 25% [5]. The experience of diagnosis and treatment of OSCC continues to be physically, mentally emotionally and financially debilitating to its victims. Thus, with regard to oral cancer, a preventive approach better fits as a solution.

Chemoprevention is defined as the use of natural, synthetic, or biologic compounds to halt, reverse, or prevent the initial phases of carcinogenesis or the progression of neoplastic cells to cancer. The inception of the concept of cancer prevention using natural or synthetic agents dates back over 80 years [6]. Chemopreventive studies have focused on oral carcinogenesis because of its established preclinical models, well defined premalignant phase and ease of monitoring.

The rationale for chemoprevention in oral cancer is provided by the concept of field cancerization which was introduced by Slaughter et al in 1953 [6]. It refers to the progressive molecular alterations occurring in clinically and histologically seemingly normal mucosa which has been chronically exposed to carcinogens in patients with or without oral cancer. The validation of this theory explains inadequacies of surgical intervention and highlights the importance of chemoprevention [7].

Oral cancer prevention methodologies are well defined owing to the fact that it has well established causative agents and risk factors, both demographic and clinical. There are three levels of oral cancer chemoprevention termed primary, secondary, and tertiary levels. Primary prevention of oral cancer involves avoiding exposure to known carcinogens such as tobacco. Secondary prevention includes early detection of cancer and well as prevention of malignant transformation of potentially malignant disorders (PMD). Tertiary cancer prevention is the prevention of occurrence and early detection of second primary tumors (SPTs) or recurrence in oral cancer patients following curative therapy [8]. Studies so far have applied oral cancer chemoprevention at the secondary and tertiary levels [9].

The literature thus far clearly indicates tobacco as a causative agent for the majority of OSCC. Thus, primary prevention in terms of eradication of this abusive substance in all its forms has the promise to reduce the incidence of OSCC dramatically [1]. However, chemoprevention can be essential in cases of PMD and prevention of occurrence of SPTs. Also in recent times, incidence of OSCC has increased in young adults and individuals with no known traditional risk factors [10,11]. Chemoprevention may hold the key in prevention of OSCC in this population.

* Correspondence to: Junaid Ahmed
E-mail: junaid.ahmed@manipal.edu

Identification and selection of chemopreventive agents in oral cancer

The multistep and multifocal process of oral carcinogenesis passes through various phases (initiation, promotion, progression) and ultimately manifests clinically as malignancy. This process is a result of cumulative effects of several biologic and molecular changes that can take several years to happen. This lengthy time span in the course of oral carcinogenesis gives scope for interventions that can halt or reverse this process.

As early as 1829 dietary nutrients were identified to play a role in prevention of carcinogenesis by Recamier. In 1925 Wolbach and Howe observed neoplastic transformation of epithelial tissues in vitamin A deficient rats and that these changes were reversed when an adequate diet was restored [6]. The relationship between nutrition and OSCC has been established with various epidemiologic studies which are the foundation for selection of micronutrients as chemopreventive agents [12].

Advances in the understanding oral carcinogenesis at a cellular and molecular level and recognition of specific genetic and epigenetic changes that occur during this process, provided rationale for chemoprevention and also identified specific targets sites for chemopreventive agents [13]. With this newfound knowledge several potential natural and synthetic chemopreventive agents (E.g. COX 2 inhibitors, EGFR inhibitors) have been identified that can halt or prevent specific molecular pathways that lead to carcinogenesis and there is hope to find more agents. Also, as no single agent can possibly block all the complex molecular and biologic interactions involved in carcinogenesis a combination of chemopreventive agents has also been tried. Combinations also have the advantage of limiting dose related toxicity and could possibly have synergistic outcomes.

In recent times retrospective epidemiological studies have led to serendipitous identification of well-known drugs (E.g.: Thiazolidinediones) as chemopreventive agents which have now been explored for OSCC chemoprevention [14].

The identification of a suitable agent is just the beginning of the selection process. Like any other medication these agents must undergo various levels of preclinical (in-vivo, in-vitro) and clinical trials (Phase I, II, III) before they can be recommended for OSCC chemoprevention.

Topical chemopreventive agents are frequently employed in the treatment of oral potentially malignant lesions as they are easy to administer with minimal systemic toxicity. However, they may not take care of the entire cancer field as they act locally [15].

Chemopreventive agents in oral cancer

More than 500 chemopreventive agents have been identified so far. Several have shown promise in preclinical trials. However, a handful of agents have had successful completion of clinical trials. In the following discussion chemopreventive agents which have undergone clinical trials in OSCC have been discussed. Also, the promising newer agents have been highlighted. Table 1 summarizes chemopreventive agents, mechanism of action and dosage.

Vitamin A and Retinoids

Retinoids were the first chemopreventive agents to be tested in oral cancer and have been extensively evaluated. These are natural or synthetic analogues or metabolites of vitamin A. Etinyl palmitate (RP) and all-trans-retinoic acid (ATRA) are natural retinoids. 13-cis-retinoic acid (13-cRA), 9-cis-retinoic acid (9-cRA), fenretinide (4-hydroxyphenylretinamide 4-HPR), are synthetic retinoids. Beta carotene, which is precursor to vitamin A has also been evaluated. Retinoids modulate cell growth, differentiation, and apoptosis in both normal and malignant cells by binding to RAR and RXR receptor types, which is their main mechanism of action [28].

Hong et al reported the first double-blind, placebo-controlled trial of high-dose 13cRA (1–2 mg/kg per day for 3 months) in treatment of oral leukoplakia. The rates of clinical response and histologic improvement were 67% and 54%, respectively in the retinoid arm and 10% in the placebo arm [29]. Subsequently several studies have been carried out to check the effectiveness of retinoids in primary chemoprevention. The major clinical drawbacks observed in these trials were significant adverse events and high recurrence rate on discontinuing treatment. The concept of bio-chemoprevention was introduced to lower the risk of recurrence and progression. In this method combination of interferon alpha, 13cRA, and alpha-tocopherol were administered to treat premalignant lesions with a 50% response rate [30] and in case of secondary chemoprevention an 84% 2-year disease free survival was observed [31]. Retinoids have also been used in secondary chemoprevention prevention, with ambiguous results.

Despite the vigorous testing of retinoids in chemoprevention, it has not been translated into clinical practice. Several factors have contributed to this. Firstly, end points in these studies i.e., clinical and histological reversal of lesion do not correlate to invasive carcinoma. This fact has been established through studies that have shown persistence of molecular abnormalities despite complete clinical and histologic response to retinoid therapy [32]. Second, the development of resistance for synthetic retinoids has been an obstacle. Third, poor accrual in these studies has also been a significant roadblock in obtaining evidence for clinical application. However, these landmark trials involving retinoids have resulted in better understanding of pathogenesis of oral cancer and also in designing of chemopreventive trials; both of which have proved to be valuable lessons.

Other micronutrients

Alpha -tocopherol (the only biologically active form of vitamin E) and Vitamin C are free radicle scavengers which

Table 1. Summary of Chemopreventive agents, Mechanism of action and Dosage

Agents	Description	Mode of Action	Dosage
Vitamin A (retinoids)	Fat soluble vitamin	-antioxidant property -induce apoptosis - cell-cycle arrest in the G1 phase -inhibit the expression of transcriptive Factor ap-1 (activator protein 1) -enhance the expression of TGF-β2 (transforming growth factor β2) -modulate histone Acetylation	**Systemic** -13cis retinoic acid (1-2 mg/kg per day) -isotretinoin (1.5 mg/kg per day) for 3 months followed by maintenance therapy (0.5 mg/kg per day) for 9 months -beta-carotene (30 mg/day) for 9 months [15-17] **Topical** -13 cis retinoic acid gel 3 times/ day for months [17, 18]
Vitamin C	Fat soluble vitamin	-protects cells from oxidative DNA damage, thereby blocking the initiation of carcinogenesis.	100–120 mg/day for adults [15,16].
Green tea polyphenols	Tea is obtained from the dried leaves of the plant Camellia sinensis	-educed COX-2 expression -activation of protein p53 - induction of apoptosis. -reduces the generation of metalloproteinase MMP-2 and -9 in cancer cells, which influences reduction of tumor invasiveness	Oral administration of green tea extracts 350 mg thrice daily for 12 weeks; up to high-dose 750 and 1000 mg/m^2 [15-17,19].
Beta-carotene	Vitamin A precursor	-antioxidant properties. -enhancement of the host immune response -decrease in DNA damage by carcinogens -inducement of morphological differentiation of cells by alteration of the adenylate cyclase system	-30 mg/d of beta carotene -1000 mg/d of ascorbic acid -800 IU/d of alpha-tocopherol [15,17].
Lycopene	Fat soluble carotenoid synthesized by photosynthetic plants and microorganisms	- antioxidant - antiproliferative and redifferentiation activities -photoprotection -anti-inflammatory -immunomodulation -Anti-angiogenesis -induction of apoptosis -interaction with growth factors	4–8 mg per day for 3 months [15,17].
Bowman-birk inhibitor	Inhibitor of serine Proteases found in soya beans.	-inhibit chymotrypsin and trypsin. -antioxidant properties -influences DNA repair, as well as the metabolism of Arachidonic acid	a single oral dose ranging from 200 to 1066 CIU/day for oral leukoplakia [16,17]. **Topical** - Bowman-Brik inhibitor concentrate mouthwash swished BID for 6 months [20,21]
Black Raspberry	Antioxidants due to high anthocyanin content	- anti-inflammatory -proapoptotic action	**Topical**: Black raspberry bioadhesive gel daily × 3 months [16,17, 22].
Bleomycin	Chemotherapy	-induces apoptosis	Bleomycin in DMSO (1%) application once daily × 14 days [16,17,23].
EGFR inhibitors	Protein belonging to the family of receptors of ERBB	-induce apoptosis -inhibitor of cancer-cell proliferation	-Erlotynib in the doses of 150mg/day, For 12 months -oral application of erlotinib, in the doses 50, 75, and 100mg [16,24].
Thiazolidinediones	antidiabetic drugs	-induction of cell cycle arrest -induces apoptosis -redifferentiation -Inhibition of angiogenesis	Piogliatazone 45 mg/day Rofecoxib 25 mg/day Troglitazone 800 mg/day Trofosfamide 50 mg t.i.d [14,25].
Cox-2 inhibitors	NSAIDS	-inhibits angiogenesis and metastasis -anti-inflammatory - induces apoptosis	Celecoxib in the doses of 100mg to 200mg, twice daily [26].
Selenium	Essential nutritional Element	-inhibits initiation and promotion phases of carcinogenesis	400 mg/day for 3 months [15].
Curcumin	Active component Of turmeric extracted from the dried rhizome of curcuma longa.	-antioxidant -anti-inflammatory properties -induce apoptosis -anti-proliferative -antiangiogenic properties	-Oral curcumin 3.6 g twice daily for 6 months effective in oral leukoplakia -curcumin 400 mg lozenges for 3 months -curcumin 500 mg with topical application of turmeric oil 12 drops (600 mg) for 6 months effective in OSMF [15,16].
Resveratrol	Component of grape Skin, red wine, berries, peanuts and many other Plants.	-cell cycle arrest -suppression of cell proliferation -induces apoptosis -induces differentiation -reduction of inflammation and angiogenesis -inhibition of adhesion. Invasion and metastasis	0.5, 1.0, 2.5, and 5 g/day for 29 days significantly reduced the levels of insulin like growth factor 1 and insulin-like growth factor binding protein 3 in plasma [15].
Aspirin	NSAIDS	-NF-κb signaling in Carcinogenesis	81–325 mg once a day [15].
Indomethacin	NSAIDS	-Antineoplastic activity at low doses. -inhibition activity on prostaglandin E2 levels, which in turn inhibit cell growth.	50 mg twice daily [15].
Lovastatin	HMG CO-A reductase inhibitors	-Reduces cellular Proliferation - induces apoptosis	7.5 mg/kg daily for 21 days and repeat therapy for every 28 days [15].
Atorvastatin	HMG CO-A reductase inhibitors	- Induces apoptosis -cell-cycle G1 arrest -autophagy, resulting in reduced cell proliferation	20 mg/night for 2 years during radiotherapy, effective in nasopharyngeal carcinoma [15].
Metformin	Anti-hyperglycemic agent	- Induces apoptosis	500–2500 mg daily [15].
Vitamin E	Fat soluble vitamin	-antioxidant property -anti-inflammatory property -inhibitor of cancer-cell proliferation and Growth -apoptosis -angiogenesis	-Alpha-tocopherol (400 IU/d) [27]. -combination of vitamin E with lycopene and selenium has been found to be an effective management strategy for oral premalignant lesions [15].

have the potential to prevent effects of carcinogens. However clinical studies of these agents, mainly in combination with other agents have not shown promising results [33].

COX2 inhibitors

Overexpression of cyclooxygenase-2 (COX2) has been shown in oral dysplasia's, OSCC and normal mucosa adjacent to the malignancies. This is said to help in the process of carcinogenesis by stimulating cell proliferation, inhibiting apoptosis, enhancing angiogenesis and prostaglandin induced inhibition of antitumor immunity [26,34]. Hence, chemopreventive abilities of both selective COX2 and non-selective inhibitors have been examined. However, trials by Mulshine et. al., [34] and Papadimitrakopoulou et. al., [26] have not shown significant results. These negative results and the cardiovascular toxicities observed with COX2 inhibitors have not encouraged further studies.

EGFR inhibitors

In OSCC, overexpression of epidermal growth factor receptor (EGFR) is seen with increased levels of transforming growth factor alpha (TGF alpha); a ligand which activates EGFR. Activated EGFR contributes to the development of a malignant cellular phenotype, including resistance to apoptosis, increased proliferation, invasion, metastasis, and stimulation of angiogenesis [35]. Thus, inhibitors of the EGFR such as gefitinib and erlotinib have been considered. Chemopreventive potential of erlotinib was evaluated by a large, randomized placebo-controlled trial which included patients with high-risk oral pre-malignant lesion with or without a prior history of curative therapy for oral cancer as determined by loss of heterozygosity (LOH). However, erlotinib treatment did not improve oral cancer-free survival in the LOH positive patients. NCT00402779 [36].

Evidence suggests that combination therapy targeting EGFR and COX2 may be efficacious as EGF and the ligand of the EGFR induce COX-2, contributing to the increased levels of prostaglandin in premalignant and malignant cells in head and neck tumors. The combination of erlotinib and celecoxib showed promising interim results in prevention of head and neck cancer; however, majority of the patients showed progress in severity on long term follow up [37].

P53-targeted agents

P53 inactivating mutations are seen in 47% to 62% of HNSCC and these mutated cells have been a target for chemopreventive agents. ONYX-015 an attenuated adenovirus has been used to eliminate cells with mutated p53 gene. Local drug therapy in the form of mouth wash [38] and intralesional injections [39] have been studied but the long-term results have not been satisfactory.

Thiazolidinediones

Diabetic patients treated with thiazolidinediones had a reduced incidence of lung and head and neck cancers in retrospective epidemiologic studies, when compared with diabetic patients receiving alternative oral hypoglycemic agents [39]. A phase II trial with pioglitazone has shown promising results [40] and has formed a basis for a larger, ongoing, multicenter, phase II b study of pioglitazone versus placebo in patients with oral premalignant lesions [41].

Natural Compounds

Many natural compounds with their high polyphenol content have been explored in chemoprevention trials.

Curcumin is the principal curcuminoid spice in turmeric, which is a member of the ginger family (Zingiberaceae). It has been consumed as a dietary supplement for thousands of years and has been considered one of the most potent anticancer agents. Phase I clinical trials have shown promising results [42], with recent trials showing improved chemopreventive effects in combination with metformin

Green tea extracts namely the polyphenol epigallocatechin-3-gallate (EGCG) has shown to modulate multiple signaling pathways like inhibition of receptor tyrosine kinases with their downstream pathways, inhibition of NF-kappa-B and activation of the p53 pathway. Tsao et al [43] have shown promising results in their study. Currently there is an ongoing trial in which EGCG is being administered with erlotinib for treatment of oral premalignant lesions. (NCT 01116336) [21].

Bowman Birk Inhibitor, a serine protease inhibitor isolated from soybeans had shown positive results in phase I and II a of clinical trials. But a recently concluded phase IIb trial has not yielded positive results [44,45].

Genistein, soy isoflavones, berry extracts have shown positive results in the pre- clinical phase and are currently undergoing clinical trials. Resveratrol, kava (Piper Methysticum), sulphoraphane**,** pomegranate juice, luteolin, lycopene, and other fruit and vegetable extract are also currently being investigated for their chemopreventive potential [46-48].

Trials and future directions in oral cancer chemoprevention

A well-designed trial is an essential perquisite to achieve success in chemoprevention. There are various challenges faced in each phase of research. The future amendments and innovations should be made with this consideration.

Pre-Clinical Phase: Although several agents show positive results in this phase, this fails to translate in a clinical setting. This partly can be attributed to difference in the pre-clinical models, especially animal models and human carcinogenesis. There is a need to close this gap to achieve more predictable clinical outcomes [49].

Clinical Phase: There are innumerable challenges in oral cancer Chemopreventive trials mainly due to the long-time frame in the process of carcinogenesis. This factor increases the cost of the trials, due to the required large sample size and long term follow-up. Identification and recruitment of high-risk patients in clinical trials will reduce the sample

size. This has been implemented in the Erlotinib Prevention of Oral Cancer (EPOC) trials [46]. Biomarkers are genetic and molecular changes related to different stages of oral carcinogenesis. If measurement of biomarker co relates with risk of developing malignancy, it can be used as a monitoring tool in clinical trials, which will help in reducing the follow up time. Thus, these biomarkers should be identified and evaluated at the pre-clinical stages of a particular trial and then should be co related clinically [46]. Poor accrual has also hampered the progress of studies [50].

Improving outcomes of chemopreventive agents: The long-term nature of treatment causes drug related toxicities, thus increasing dropout rates in trials. Thus, there is need to find agents with minimal or no toxicity on long term use or find improved methods of drugs delivery which enhance efficacy. Nanoparticles, microspheres and mucoadhesive patches are some of the modalities currently being investigated [51-53]. As tumors can have diverse genetic and epigenetic changes, a personalized approach to cancer prevention could get us closer to more effective intervention strategies.

Conclusion

Over two decades of research in the field of oral cancer chemoprevention have yet to yield clinically applicable results. However, these projects have expanded our knowledge about various aspects of oral cancer. This modality of prevention of cancer has shown potential to succeed and only rationally designed trials hold the answers. The amalgamation of various aspects such as advances in understanding of pathogenesis of oral cancer, more efficient methods for identification of high-risk population, discoveries of new chemopreventive agents, innovative methods of drug delivery which maximize the beneficial outcomes and recognition of appropriate biomarker end point for effectively monitoring clinical trials; will propel oral cancer chemoprevention towards its goal. Individualized target therapy approach seems to be the future of oral cancer chemoprevention. Until this has been achieved primary prevention is the only potent method of oral cancer prevention.

Authors' contribution

NS: conception and design, acquisition of data, analysis, and interpretation of data, drafting the article, final approval of the version to be published

PG: revising the article, acquisition of data, analysis of data, final approval of the version to be published

JA, AS, NS: drafting the article, interpretation of data, final approval of the version to be published

YC: conception and design, acquisition of data, drafting the article, final approval of the version to be published.

Conflict of interest

None to declare.

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