Oral Cancer and Chemoprevention

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ABSTRACT: Oral cancer is one of the major global threats to public health. The development of oral cancer is a tobacco-related multistep and multifocal process involving field cancerization and carcinogenesis. As, curative therapy available for oral cancer often results in debilitating changes in appearance, speech, swallowing and breathing, preventive strategies are desirable. Chemoprevention, is the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression. Chemoprevention holds promise in the management of oral cancer. Many agents have been tried as chemopreventive agents such as retinoids, betacarotene, dietary factors and vit. E. The present article reviews the various aspects of chemoprevention and various chemopreventive agents used.

Keywords: Chemoprevention, oral cancer, premalignant lesions.

I. INTRODUCTION

These days the world is heading towards various types of non communicable diseases, which are also known as modern epidemics. Among these modern epidemics, cancer is the second commonest cause of mortality in developed countries\textsuperscript{1}. In the developing countries cancer in among the three leading causes of death for adults.\textsuperscript{2}

Cancer, which is defined as abnormal growth of cell and can affect any tissue or organ of body.\textsuperscript{3}

The term oral cancer is used to describe any malignancy that arises from oral tissues. Ninety to ninety five percent of all oral malignancies are squamous cell carcinoma.\textsuperscript{4}

Oral cancer is one of the most common cancers in the world and a major public health problem in developing countries including India. Smoking, drinking and chewing tobacco have been positively associated with oral cancers since long. This implies that oral cancer is a self-induced disease, which is amenable to primary prevention.\textsuperscript{5}

Though primary prevention holds appropriate in the perspective of oral cancer since curative therapies are associated with serious complications.\textsuperscript{6} The success of several clinical trials in cancer prevention in high-risk populations suggests that chemoprevention is a rational and appealing strategy. Cancer chemoprevention is very attractive and has earned serious consideration as a potential means of controlling cancer incidence. Currently, the National Cancer Institute (NCI) has made chemoprevention research a top priority; more than 400 potential agents are currently under investigation.\textsuperscript{7}

Cancer chemoprevention, was first defined in 1976 by Sporn, is the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression.\textsuperscript{8} Chemoprevention in oral cancer has been directed toward reversing premalignant lesions and preventing second primary tumors (SPT). Interfering with the carcinogenic process early in the pathway before malignant transformation and preventing second primary lesions represents a striking approach for reducing the incidence and related morbidity and mortality of oral cancer.

Oral cancer is an ideal model to consider chemo-preventive strategies for following reasons: It has known etiologic factors, namely tobacco, alcohol, betel nut chewing and viruses.\textsuperscript{9} There is a strong proven association with established premalignant lesions, such as leukoplakia, erythroplakia and oral submucus fibrosis. It has a well defined tumor progression model in which cancer progresses from normal epithelium to mild, moderate and severe dysplasia to carcinoma \textit{in situ} and frank invasive cancer. The lesions can be effectively screened and can be subjected to histopathological examination before and after the usage of chemopreventive agents. It is generally accepted that a dysplastic lesion carries a decisively greater risk of malignant transformation than a non dysplastic one.
Chemopreventive agents are directed toward secondary preventive stage where appropriate action can be directed toward early precursor lesions like leukoplakia. Intervention at this stage will reduce the morbidity and mortality associated with the oral cancer and also will not add financial burden to the patients.

II. MECHANISM OF ACTION OF CHEMOPREVENTIVE AGENTS

Oral cancer develops as a multistep, multifocal disease as a result of various carcinogenic insults on oral mucosa. Carcinogenesis can be defined as a multistage process involving a genetic or epigenetic damage in susceptible cells that gain a selective growth advantage and undergo clonal expansion as a result of activation of proto-oncogenes or inactivation of tumor suppressor genes or both. The proto-oncogenes produce proteins that control growth at one or more steps by forming an intracellular communication network in the growth signaling pathway. When proto-oncogenes are altered, a modified gene called an oncogene is formed. Proto-oncogenes can be converted to oncogenes by genetic mutation and overexpression. The cyclin group of proteins is important because they drive the cell through the cell cycle. Alterations of the cyclin-D1 gene and its protein product have been identified in the head and neck cancers. Oncogenes are associated with carcinogenesis. Carcinogens are agents which can induce cancer. The most common carcinogen which induces oral cancer is tobacco. Tobacco smoke contains a large number of chemical carcinogens, including aromatic hydrocarbons, such as benzantracene and benzopyrene and nitrosamines, such as nitrosonormicotine. These carcinogens have been shown to induce specific genetic changes of the p53 and H-ras genes. Oral cancer follows the molecular progression model in specific molecular events, including oncogene activation and inactivation of tumor suppressor genes, leading to progression from normal cell growth to frank neoplasia and tumor formation. The lesions often start as a potentially malignant lesion that may be a clinically apparent or innocuous, such as leukoplakia. Over the years it undergoes series of genetic alterations and progresses through well-defined pathological stages to invasive squamous cell carcinoma. Oral cancer prevention essentially involves reversal or suppression of the carcinogenesis process. The rationale of trying chemopreventive agents lies in the concept of field cancerization. Field cancerization model was proposed by Slaughter et al in 1953. They proposed that carcinogenic exposure of the entire oral mucosa predisposes to the development of frank neoplasm at multiple sites within the oral cavity. Oral cancer prevention essentially involves surgical and therefore local surgical removal of involved site fails to stop the progression toward malignancy.

III. IDEAL REQUIREMENTS OF CHEMOPREVENTIVE AGENTS:

An ideal chemopreventive agent should have:
1) little or no toxicity;
2) high efficacy in multiple sites;
3) capability of oral consumption;
4) known mechanisms of action;
5) low cost, and human acceptance.

IV. CLASSIFICATION OF CHEMOPREVENTIVE AGENTS

Pharmacological and chemical structural classification of promising chemopreventive agents. 
1. Antimutagens/carcinogen blocking agents
   – Phase II metabolic enzyme inducers
   – N-acetyl-L-cysteine
   – Polyphenols
   – Curcumin, dehydroepiandrosterone (DHEA)
2. Antiproliferatives
   – Retinoids/Carotenoids: β-carotene, 13-cis-retinoic acid, vitamin A.
   – Glucose-6-phosphate dehydrogenase inhibitors
   – Aspirin
3. Antioxidants

V. COMMONLY TRIED CHEMOPREVENTIVE AGENTS IN ORAL CANCER

- Vitamin A and other retinoids
- Beta-carotene
- Vitamin E
- Dietary agents
- Newer agents

5.1 Retinoids

Retinoids have been widely studied as chemopreventive agents. They have been shown to induce apoptosis, to suppress carcinogenesis, to decrease growth rate of epithelial cells, and to reduce free radicals.
Retinoids regulate transcription via the activation of specific retinoid receptors, and also have a role in suppressing the activity of other transcriptional factors, such as the activator protein-1 (AP-1). This molecule mediates the signal from growth factors, inflammatory peptides, oncogenes and tumor promoters, and results in cell proliferation.

In 1986, Hong et al conducted a prospective, randomized, double-blind clinical trial in 46 oral leukoplakia patients. He reported that those who received high-dose of 13-cis-retinoic acid had significant clinical improvement in retinoid arm as compared to placebo. The rate of histopathologic improvement was also significantly higher in the retinoid arm. But the major clinical limitations included a high rate of relapse and toxicity, which included dry skin, conjunctivitis, cheilitis, and hypertriglyceridemia. In another trial, Koch achieved complete or partial remissions in 45% of patients with premalignant lesions treated with 1 of 3 retinoids—13cRA (isoretinoin), trans-beta-retinoic acid, or aromatic retinoid—after follow-up of up to 6 years.

In Milan, Italy, in 1988, Chiesa et al began a randomized trial to evaluate the efficacy of systemic synthetic retinoid 4-HPR as maintenance therapy versus no intervention after complete laser resection of oral leukoplakia. 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. 4-HPR was well tolerated, and toxicity was minimal.

5.2 Vitamin A

Vitamin A is essential for the development and maintenance of normal epithelium. Vitamin A deficiency causes a change in the differentiation pathway, resulting in epithelial hyperplasia and squamous metaplasia. Epidemiologic surveys suggest that the risk of oral carcinogenesis is increased with vitamin A deficiency. The mechanism underlying the chemopreventative effects of vitamin A and its derivatives is the restored expression of retinoic acid receptor-beta (RAR-b) mRNA, which promotes normal tissue growth and differentiation.

Subsequent trials have confirmed the activity of vitamin A in oral leukoplakia. In India, Stich et al compared vitamin A (200,000 IU/wk orally for 6 mo) 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.

5.3 Beta Carotene

Beta carotene is a naturally occurring, nontoxic carotenoid with biologic properties that may be suitable against oral leukoplakia. Results of some trials indicate that beta carotene has substantial activity in oral premalignancy.

Garewal et al described a high response rate in a phase II trial of beta carotene in leukoplakia. Twenty-four patients who could be evaluated were treated, 17 of whom had major responses (2 complete, 15 partial), for a response rate of 71%.

In another phase II study of beta carotene in oral leukoplakia, conducted by Suda et al in 1989, the response rate was 44.4%. No significant toxicity occurred that required drug discontinuation or dose reduction.

Sankaranarayanan et al conducted a double-blind, placebo-controlled trial to evaluate the chemopreventive potential of either vitamin A alone or beta carotene alone in patients with oral leukoplakia in India. In their study, 160 patients with oral precancerous lesions received either oral vitamin A or beta carotene for 12 months. The complete regression rates were as follows: 10% in the placebo group, 52% in the vitamin A group, and 33% in the beta-carotene group.

In a study by Kaugars et al, 79 patients with oral leukoplakia received 30 mg/d of beta carotene, 1000 mg/d of ascorbic acid, and 800 IU/d of alpha-tocopherol for 9 months. Clinical improvement of the oral lesion was noted in 55.7% of the patients. The advantage of carotenoids is that they are relatively non toxic.

5.4 Vitamin E

The term vitamin E describes a family of light antioxidants, four tocopherols (alpha-, beta-, gamma and delta-). Alpha-tocopherol is the only form of vitamin E that is actively maintained in human body. Vitamin E (alpha-tocopherol) is a potent antioxidant that neutralizes free oxygen radicals and inhibits 2 carcinogenic nitrosamine formation. They have been reported to block the in vivo formation of N-nitroso compounds and suppress chemical carcinogenesis in animals. They may inhibit cancer development through several mechanisms like stimulation of wild-type p53, down regulation of mutant p53, activation of heat shock proteins, and an antiangiogenic effect mediated by blockage of transforming growth factor-alpha.

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The antioxidant vitamin E (α-TF) prevented the development of cancers in oral cavities in animal studies. A phase II study by Benner et al.[23] showed that among 43 patients with oral leukoplakia who took 400 IU of vitamin E twice daily for 24 weeks, 46% had clinical responses and 21% had histological responses. The treatment was well tolerated, without any toxicity, and with good compliance.

5.5 DIETARY AGENTS

A variety of grains, cereals, nuts, soy products, olives, beverages confer a protective effect against cancer.[24] In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen containing as well as organosulfur compounds, which have shown to suppress early and late stages of carcinogenesis.[25]

Recently, the bioactive triterpene, lupeol, commonly found in fruits like fig, mango, etc., has attracted interest in the context of chemoprevention attributable in large part to its antioxident,[26] anti-apoptosis- inducing and antiproliferative anti-mutagenic, anti-inflammatory[27] properties as well as its efficacy in inhibition of in vivo and in vitro cancer growth. Triterpenes represent a varied class of natural products, which occur commonly and are found in fruits, vegetables and other parts of several medicinal plants e.g., Arbutus unedo, Tipuana tipu, etc.[28] have seen tremendous efforts by researchers worldwide to develop this wonderful molecule as a chemopreventive agent.

5.5.1 Curcumin

A spice widely used in Indian cuisine, has been identified to show considerable anti-tumor effects. It is a yellow pigment that is present in the rhizomes of turmeric (Curcuma longa L.) and related species and is one of the most extensively investigated phytochemicals, with regard to chemopreventive potential. The mechanisms implicated in the inhibition of tumorogenesis by curcumin are diverse and appear to involve a combination of anti-inflammatory, antioxidant, immunomodulatory, proapoptotic, and antiangiogenic properties via pleiotropic effects on genes and cell-signaling pathways at multiple levels. When curcumin is combined with some cytotoxic drugs or certain other diet-derived polyphenols, synergistic effects have been demonstrated.[29] A late finding is that curcumin binds directly to and activates VDR (the nuclear vitamin D receptor), inducing the VDR target genes CYP3A4, CYP24, p21 and TRPV6.[30] Despite our increasing knowledge on this substance there still remain many unknown effects that deserve intense investigation.[31]

5.5.2 Gingerol

A phenolic substance that is responsible for the spicy taste of ginger (Zingiber officinale) was reported to inhibit tumor promotion and PMA-induced ornithine decarboxylase (ODC) activity and TNF production in mouse skin.[32]

5.5.3 Epigallocatechin gallate (EGCG)

It is an antioxidant and chemopreventive polyphenol that is found in green tea. It has been shown to suppress malignant transformation in a PMA-stimulated mouse epidermal JB6 cell line, which seemed to be mediated by blocking activation of Ap1.[33]

5.6 Newer Agents

Progress in molecular biology has made it possible to identify the genotypic alterations that lead to the development of malignant clones and molecular markers of specific stages in multistep carcinogenesis. Potential new targets for chemoprevention, which are under consideration in oral cancer, include the following: H-ras gene, epidermal growth factor receptor (EGFR) inhibitors, p53 gene, COX-2 inhibitors, NF-KB.[34,35] Both EGFR signaling and COX-2 expression are deregulated in neoplasia. Activation of either EGFR signaling or increased production of COX-2-derived prostaglandins can impact several mechanisms that have been linked to carcinogenesis, including cell proliferation, apoptosis and angiogenesis.

VI. CONCLUSION

Human oral cancer is the sixth largest group of malignancies worldwide. Seventy percent of oral cancers appear from premalignant lesions. The process of formation of oral cancer results from multiple sites of premalignant change in the oral cavity (field cancerization). The weed of the oral cancer can be destroyed before it spreads and this can be achieved by chemoprevention. Chemoprevention also has an impact on the development of malignant changes in the oral mucosa. Prevention through chemoprevention and/or the use of systemic medications is an extensively studied strategy and continues to hold promise as a way of diminishing the morbidity and mortality associated with this malignancy.
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