ABSTRACT

Oral cancer is one among the ten most common cancers in the world and shows a marked geographic variation in occurrence. It causes considerable morbidity and is associated with a 5-year survival rate of less than 50%. Current treatment primarily consists of surgery and radiotherapy and improvement in long-term cure rates with these modalities has reached a plateau. As, curative therapy available for oral cancer often results in debilitating changes in appearance, speech, swallowing and breathing, preventive strategies are desirable. Cancer chemoprevention is the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression. Chemoprevention has been an extensively-studied strategy and continues to hold promise in the management of oral cancer. Many agents have been evaluated as possible chemopreventive agents including vitamin A and retinoids, beta-carotene, vitamin E and dietary agents. Recently, molecularly targeted approach has generated interest among researchers worldwide which includes cyclooxygenase-2 (COX-2) inhibitors, EGFR inhibitors and adenovirus vectors. This article reviews the various aspects of chemoprevention and describes important chemopreventive agents and design of chemopreventive trials.

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INTRODUCTION

Cancer is an increasingly prevalent disease globally that accounts for immense morbidity and mortality per annum. Various treatment options are available which includes surgery, radiotherapy and chemotherapy which are used either singly or in combination depending upon the clinical stage of the disease. There is an old saying ‘Prevention is better than cure’ that holds appropriate in the perspective of oral cancer since curative therapies may be associated with serious oral complications. Hence, role of preventive strategies could be a major breakthrough in management of oral cancer.

Cancer chemoprevention, as first defined in 1976 by Sporn, is the use of natural, synthetic or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression. Presently, cancer institutes all over the world are trying newer chemopreventive agents which would set a new dimension in the management of oral cancer.

LEVELS OF PREVENTION

Prevention of oral cancer can be broadly divided into three phases which includes primary, secondary and tertiary levels of prevention. Primary prevention is stoppage of risk factor exposure, such as tobacco and includes educating the general population about the potential ill effects associated with tobacco and also training clinicians to counsel patients about risk factors associated with oral cancer. Primary prevention strategies are aimed toward prevention at grassroots level and are meant toward addressing the root cause of cancer. This calls for a complete overhaul of the national cancer control program with strong emphasis on primary prevention of major cancers in the country.

There are two major aspects of primary prevention program: Legislation and education. Legislation should be enacted to make the sale of tobacco under check and place health warning signs wherever, tobacco products are sold and place health warning signs on packets containing these products. There has been a lot of debate regarding the role of government in formulating antitobacco policies. The regulation stating depiction of pictorial warnings on cigarette packets is also farcical, as most cigarette packets come with a small picture of a blurred chest radiograph, which even a trained clinician can barely interpret. Surrogacy of tobacco advertisements via pan masala advertisements has been a proven fact and just adds fuel to the fire. A health education program should combine various techniques, such as person-to-person communications, person-to-group communication and the mass media. Secondary prevention involves patients who have known potentially malignant lesions (i.e. oral leukoplakia) and attempts to prevent the progression of the premalignant lesions into cancers. Secondary prevention refers to early diagnosis and intervention, which includes early recognition and treatment of premalignant lesions. Efforts at early detection can take many forms. The simplest way is to educate and encourage individuals to examine their own mouth that is self-examination. World Health Organization recommends that primary health workers should be trained to search for oral precancerous lesions, when they seek high-risk individuals. 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.
Tertiary prevention focuses on the prevention of second primary tumors in patients treated for cancer or their precursor states. Tertiary prevention involves reduction of complications, prevention of further dysfunction and reduction of long-term complications of disease, including speech, dental and swallowing problems.7

MECHANISM OF ACTION OF CHEMOPREVENTIVE AGENTS

Oral cancer develops as multistep, multifocal disease as a result of various carcinogenic insults on oral mucosa. Carcinogenesis can be defined as 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 nitrosornorharicine. These carcinogens have been shown to induce specific genetic changes of the p53 and H-ras genes.8 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.1,9 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.10 The multiple site involvement makes it difficult to intervene surgically and therefore local surgical removal of involved site fails to stop the progression toward malignancy.

CHEMOPREVENTION IN ORAL CANCER

Chemoprevention is defined as the administration of agent(s) to block or reverse carcinogenesis. 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 chemopreventive strategies for following reasons: It has known etiologic factors, namely tobacco, alcohol, betel nut chewing and viruses.3 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 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 nondysplastic one.

CLASSIFICATION OF CHEMOPREVENTIVE AGENTS

Pharmacological and chemical structural classification of promising chemopreventive agents.11

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

COMMONLY TRIED CHEMOPREVENTIVE AGENTS IN ORAL CANCER

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

In the head and neck region, retinoids have shown promise as chemopreventive agents, but they produce significant side effects, making them less than ideal chemopreventive agents. Several other agents have a significant potential to become safe, effective alternatives to the retinoid and are under active investigation.

**Vitamin A and other Retinoids**

Vitamin A and its derivatives, known collectively as the retinoids, have been some of the most extensively studied agents for the chemoprevention of oral cancer. The natural retinoids play a role in essential biological processes, including vision, metabolism, growth, differentiation, hematopoiesis, immunological processes, bone development and embryogenesis. The principle mechanism of action of retinoids lies in their ability to suppress the cell proliferation by blocking cell cycle transition or by inducing apoptosis. 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. Retinoids may also induce tumor cells to differentiate or undergo apoptosis. Although the clinical efficacy of retinoids has shown promise in several trials but the exact molecular mechanism is yet to be determined.

Retinoids have been tried as chemopreventive agents in potentially malignant disorders such as leukoplakia which frequently develops into invasive squamous cell carcinoma. Although the mechanism of action of retinoids in chemoprevention of oral cancer is not well established, several trials have been carried out to evaluate their clinical efficacy and are one of the most tried chemopreventive agents in oral cancer.

The trial reported by Hong et al showed promising results in this direction. The investigators tested the activity of 13-cis-retinoic acid in a randomized, placebo-controlled double-blind trial involving 44 leukoplakia patients. Around 67% of the patients had an objective clinical response to the therapy, and 54% had a histological response. In contrast, patients receiving placebo had only a 10% objective response rate. However, substantial toxicity and a high rate of relapse after discontinuation of the treatment presented major clinical limitations to this high dose trial. Lippman et al investigated low dose of 13-cis-retinoic acid to address the toxicity and relapse problem of trial reported by Hong et al. Ninety percent of the patients showed regression of the lesion and this low dose 13-cis-RA was well tolerated, with no patients dropping out because of toxicity. To assess the chemopreventive effects of vitamin A (retinyl palmitate) and N-acetylcysteine, a large randomized intervention study, the euroscan trial, was undertaken. In the euroscan trial, 2,592 patients were randomly assigned to receive retinyl palmitate (300,000 IU daily for 1 year followed by 1,50,000 IU for a 2nd year), N-acetyl cysteine (600 mg daily for 2 years), both compounds or no intervention. A 2-year supplementation of retinyl palmitate and/or N-acetylcysteine resulted in no benefit—in terms of survival, event-free survival, or second primary tumors—for patients with HNSCC or with lung cancer. Bolla et al have studied the effect of the synthetic retinoid etretinate on development of second primary tumors following head and neck cancer. When compared to the trial of Hong et al this trial had more patients and included only patients who were treated for early stage disease. The analysis was performed after a mean follow-up period of 65 months and did not show a difference between the retinoid and placebo group.

Various trials suggest that the chemopreventive and chemotherapeutic effects of retinoids have been limited till now. However, better clinical response can be achieved when treatment is extended to a longer and even to a lifelong period.

**BETA-CAROTENE**

Carotenoids are a class of plant derived compounds that are precursor molecules to vitamin A and are found in high quantities is green and yellow leafy vegetables. β-carotene is the most plentiful of the carotenoids. Carotenoids have antioxidant activity which explain its role as a chemopreventive agent. Carotenoids also have immunoenhancing effects and act by converting to retinol. There are several trials carried to test the safety and efficacy of carotenoids as a chemopreventive agent.

Zheng et al conducted studies on nutrient levels in the blood and suggested that deficiencies in carotenoids and vitamin E are associated with increased risk for oral and pharyngeal cancers. Garewal et al conducted a small single arm study of 24 patients who presented with leukoplakia and showed a complete and partial response rate of 71% to a regimen of beta-carotene 30 mg daily for 3 months, followed by an additional 3 months of treatment in responding patients, with no significant toxicity reported. Mayne et al in their randomized, placebo-controlled trial that enrolled 264 patients who had definitively treated oral cavity, pharyngeal or laryngeal cancer showed no benefit from 50 mg of beta-carotene daily in overall survival, local recurrences, or development of second primary tumors. The advantage of carotenoids is...
that they are relatively nontoxic, with most common side effect being yellow discoloration of the skin.

**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 and its main function is that of an antioxidant. 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 showed that among 43 patients with oral leukoplakia who took 400 IU of vitamin E twice daily for 24 weeks, 20 (46%) had clinical responses and nine (21%) had histological responses. The treatment was well tolerated, without any toxicity, and with good compliance.21

Gridley et al conducted a population-based case-control study, using a variety of vitamin and mineral supplements and found that vitamin E was the only supplement consistently associated with a lower risk for oral and pharyngeal cancers.22 Recent results of large multicenter, double blind, randomized placebo-controlled chemoprevention trial by Bairati et al for patients treated with radiation therapy for stage 1 or 2 squamous cell carcinoma of the head and neck have shown no benefit from vitamin E. The proportion of patients free of second primary cancers after 8 years was similar in treated and placebo group.23

Most of the studies have used vitamin E in combination therapy with other agents. Further studies of vitamin E alone would be necessary to better define its effectiveness as a sole chemopreventive agent.

**DIETARY AGENTS**

Recently, much attention has been focussed on fruits and vegetables with potent antimutagenic and anticarcinogenic properties. Case-control studies suggest a reduced risk of oral premalignant lesions and oral cancer with greater consumption of fruits and vegetables, but results are inconsistent, particularly for oral premalignancies. A recent meta-analysis of nine case-control studies of oral and pharyngeal cancer determined that higher fruit intake was associated with a decreased risk, but there was no consistent association with vegetables. In chemoprevention studies, supplements of nutrients commonly obtained from fruits and vegetables, such as β-carotene and lycopene, have been shown to increase likelihood of regression of leukoplakia. Maserejian et al prospectively evaluated fruit and vegetable consumption and the incidence of oral premalignant lesions among 42,311 men in the health professionals follow-up study. They concluded that the risk of oral premalignant lesions was significantly reduced with higher consumption of fruits, particularly citrus fruits and juices, while no consistent association was apparent with vegetables. It can be concluded that although the exact nutrients in fruits and the mechanism of prevention of oral premalignancy are still to be determined, dietary recommendations to increase consumption of fruits are appropriate for preventing oral precancer and cancer.24

**LYCOPENE**

Lycopene is the most abundant carotenoid in tomatoes (lycopersicon esculentum L) with concentrations ranging from 0.9 to 4.2 mg/100g depending upon the variety. Lycopene is acidic and lacks a β-ionone ring, has no pro-vitamin A activity which sets its biochemistry apart from carotenes such as β-carotene. Lycopene is rapidly destroyed by oxidation and by free radicals, such as OH and various peroxy radicals. This reactivity of lycopene is the basis for its antioxidant activity in biological systems that might contribute to its efficacy as a chemopreventive agent.25 Till date, no phase III studies of lycopene and cancer prevention have been reported.

**CURCUMIN**

Curcumin is a polyphenol derived from the plant Curcuma longa, commonly called turmeric. The primary bioactive constituents in turmeric have been found to be phenolic curcuminoids, the most important of which is curcumin. Curcumin protects cells against free radicals that promote cancer by damaging DNA and activating genes. Analysis of the structure revealed the presence of beta–diketone moiety and phenolic hydroxyl groups that are believed to contribute in antioxidation.26,27 Goel et al have demonstrated anti-inflammatory properties of curcumin to be attributable to suppression of prostaglandin synthesis and inhibited expression of COX-2.28 This finding was congruous with reports obtained in similar studies conducted by Plummer SM, Chen and RC Lantz.29 In a similar study of 3 months duration, Cheng et al10 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. Previous study by Cheng et al showed one of seven patients with oral leukoplakia developed frank malignancy in spite of curcumin treatment. In view of its important anticancer pharmacological properties various phase two clinical studies are underway to evaluate its efficacy as a chemopreventive agent.
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. 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.

CONSIDERATIONS IN DESIGN OF CLINICAL STUDIES

Chemoprevention trials are based on the hypothesis that interruption of the biological processes involved in carcinogenesis will inhibit this process and, in turn, reduce cancer incidence. This hypothesis provides a framework for the design and evaluation of chemoprevention trials that assesses efficacy and safety of chemopreventive agents. Major obstacles to overcome in designing clinical trials are the relatively low incidences and long latencies of cancers in the general population and therefore difficult to evaluate endpoint result. To prove or disapprove any chemopreventive agent(s) efficacy requires large number of subjects and long-term follow-up.

Chemopreventive trials should be targeted toward early premalignant lesions rather than frank neoplasm. As chemopreventive agents are administered over a long period, it is very critical to determine the effective dose that provides the greatest efficacy with least side effects. This can be accomplished by extensive dose titration and pharmacokinetic studies in both phase I and II trials. One strategy that increases efficacy and lessen toxic reactions is using combination therapy. Combination employs two agents with different mechanisms of activity or with additive activity. Such improved activity may allow either or both the agents to be administered at lower doses, thereby reducing potential toxicity.

Chemoprevention clinical trials need to be designed around the setting in which the patients are normally seen. Chemopreventive treatment should not interfere with other medications, surgical procedures, and monitoring the patients may be receiving.

CONCLUSION

Since cancer is like a weed that runs wild at the expense of others, it is best to destroy its seeds before they have chance to grow and spread. Chemoprevention provides an opportunity in achieving this aim, by arresting and reversing neoplastic progression before invasive carcinoma develops. An improved understanding of the process of oncogenesis has led to strategies that take advantage of the mechanisms involved in development of cancer. Oncogenesis is a multistep process occurring over a number of years, and in the head and neck the entire mucosal surface is exposed to carcinogenic agents (field carcinization). In the future clinical chemoprevention will require further development of trials based on a mechanistic understanding of carcinogenesis.

REFERENCES


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