ABSTRACT

Oral cancer holds the eighth position in the cancer incidence ranking worldwide, with squamous cell carcinoma encompassing at least 90% of all oral malignancies. The World Health Organization expects that prognosis for many of these patients is grave and even in cases of successful treatment the degree of dysfunction and disfigurement postoperatively is well appreciated by all of us. Hence, understanding of the disease process is of paramount importance for early diagnosis and successful management. Dietary substitutes, such as beta-carotene, provitamin A, vitamin A, C, and E, lipoic acid, zinc, selenium and Spirulina use in premalignant lesions, in premalignant conditions is still a debate.

The antitumor activity of micronutrients is by their capability of destroying cancer cells through three major mechanisms: (i) Tumor inhibition by immune cytokines; (ii) stimulation of cancer suppressor genes, such as ‘wild-type p54’ and diminished expression or dysregulation of oncogenes, such as mutant p53 and H-ras; (iii) inhibition of angiogenesis-stimulating factors, such as transforming growth factor alpha (TGFα).

Studies have shown that antioxidants are not the ‘magic bullet’ for the treatment of premalignant oral mucosal lesions or the prevention of second primary malignancies. However, there is a role for antioxidants if used judiciously in selected cases that can be monitored carefully. An important principle is that the treatment should not be more harmful than the damage that the lesion can cause.

Keywords: Vitamin A, Premalignant lesions, Free radicals.

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INTRODUCTION

We as an oral medicine professionals know that mouth is the mirror of the body and mind. In our body all the cells are interdependent of their function and oral cavity nourishes every part of the body. Similarly, oral cavity is exposed to lot of carcinogen and is prone to develop precancerous lesions and condition which may turn to oral cancer. Incidence rate is very high in Indian population. Around 90% of oral cancers in India are due to tobacco. Dietary substitute play a vital role in prevention of oral cancer.

These dietary substitutes are beta-carotene, provitamin A, vitamin A, C and E, lipoic acid, zinc, selenium and Spirulina. All these are obtained from plant or animal source, i.e. mainly liver, animal meat, milk, egg and yellow/orange vegetables. The functions of antioxidants are to remove free radicals from the body and as a result prevent cell damage or mutation in gene. Antioxidants are the products which are derived mainly from vegetables/food grains, animal fats/vitamins and also from spices like curcumin (tamin) or garlic. These antioxidants can protect the human population from premalignant lesions and oral cancer.

OXIDATION AND FREE RADICALS

As the amount of oxygen gradually increased over the past 1 billion years in the earth’s atmosphere, the advantage of oxidative (aerobic) as compared with anaerobic metabolism became greater because of its ability to produce energy from food more efficiently. This favored the development of more complex organisms, but there was also a need to develop systems to protect cells against the potential harmful effects of oxygen. At the atomic level, oxidation causes the loss of an electron and produces free radicals, which are unstable atoms or molecules with one or more unpaired electrons.

Free radicals quickly interact with surrounding atoms and produce even more free radicals in an attempt to stabilize them by attracting other electrons. Cellular mutations can arise when free radical damage occurs within the nucleus of a cell and affects the DNA. Oxidation and production of free radicals are normal functions of cells using oxidative metabolism, and, in a balanced situation, host antioxidant defences prevent cellular damage. However, an excessive number of free radicals are harmful; as an example, much of the cellular damage from ionizing radiation is caused by the production of too many hydroxyl free radicals.1

The frustration of how to effectively treat premalignant oral lesions and the need to prevent second primary oropharyngeal cancers have promoted research interest into how antioxidants might be used clinically. The possible uses of antioxidants for oral mucosal lesions include: (i) Prevention of lesions in high-risk individuals with mucosa that clinically appears normal and with no history of either premalignant or malignant oral lesions. (ii) In order to prevent recurrence of the treated initial lesion or to prevent the development of a second primary.

VITAMIN A

The term vitamin A is usually used to refer to both the metabolically active form (retinol) and other chemical forms that are converted into retinol within the body (carotenoids). Retinol is called preformed vitamin A, and the carotenoids, of which beta-carotene is the most active, are called provitamin A. Dietary sources of retinol are primarily animal.
products and include milk, butter, egg, liver and fish. Carotenoids are found in vegetables and fruits. The clinical effects of vitamin A deficiency are related to the increased keratinization of epithelia throughout the body. Metaplasia of the epithelium is also noted with vitamin A deficiency and may be a precursor to premalignant and malignant epithelial changes. Administration of vitamin A to a deficient patient affects the basal cell layer of the epithelium so that there is a return to the production of nonkeratinized epithelium. The first study that associated vitamin A deficiency with human cancer was published in 1941.

Retinoids

The term retinoid indicates one of the more than 200 synthetic or natural derivatives of retinol. Only a few have been extensively investigated and the most widely known clinical retinoid is 13-cis-retinoic acid (isotretinoin, Accutane) (13-cRA), which was approved in 1982 in the United States for the treatment of severe acne. ‘13’ refers to the carbon position of the carboxyl group and ‘Cis’ indicates the type of stereoisomer.

USE WITH ORAL LESIONS

Silverman et al evaluated vitamin A supplements in the treatment of oral leukoplakia as early as the 1960s. Although their use of vitamin A ester troches had some clinical success, most of their patients had side effects, and the clinical responders typically relapsed shortly after discontinuing the troches. Five of the 16 patients with oral leukoplakia treated by Shah et al5 dropped out of a program using 13-cRA. Three of the remaining patients had complete resolution of their lesion, but the lesions in two of the patients recurred within 5 weeks after discontinuing the 13-cRA. This pattern of some patients not being able to tolerate the side effects of 13-cRA, which include dry skin, cheilitis, xerostomia, hypertriglyceridemia, and teratogenic effects and the recurrence rate after discontinuation has been repeated in other studies.

Hong et al published an article in 1986 on the use of 13-cRA that is generally credited with generating much of the interest in using retinoids for the treatment of oral leukoplakia. Their study reported that 67% of a group of patients with oral leukoplakia had more than a 50% reduction in the clinical size of their lesions after 3 months of taking 1 to 2 mg of 13-cRA/kg of body weight/d, but 79% of the patients experienced side effects. Later studies reduced the 13-cRA dose and found a similar rate of clinical success but with a reduction in the severity of the side effects. An open trial of 13-cRA used in the treatment of chronic oral leukoplakia that were at least 2 cm in diameter demonstrated some success because three of the 10 patients showed more than 50% reduction in the size of their lesions. However, the side effects led to a decrease or discontinuation of the 13-cRA in most of the patients.

Surgical removal is the treatment of choice for oral leukoplakia, and 13-cRA should be reserved for patients who have a recurrence after surgical excision, when the lesion is large, or when surgical removal is not possible because of patient or lesion factors. One advantage of 13-cRA is that the clinical results are generally apparent within 30 to 60 days, and if there is no improvement, then it can be discontinued.

Garewal and Meyskens have stated clearly the position that the treatment of an oral lesion should not cause more harm to the patient than the possible sequelae of the lesion. Therefore, it is difficult to justify the use of 13-cRA in cases of hyperkeratosis without epithelial dysplasia or mild epithelial dysplasia because of the low probability of malignant change in the lesion, the high incidence of side effects and the recurrence rate after discontinuation.

Oral lichen planus has been treated with etretinate (Tegison), which is a synthetic retinoid, but the clinical success was inconsistent and the relapse rate was more than 50% within 3 months.

Prevention of a Second Primary Oropharyngeal Carcinoma

Patients who have been successfully treated for squamous cell carcinoma of the oral cavity still face a 5% annual risk for the remainder of their lives of developing a second and separate primary oropharyngeal carcinoma. The probability of a second primary cancer exceeds that of a recurrence approximately 4 years after the diagnosis of the initial carcinoma. An initial study published by Hong et al showed that 50 to 100 mg of 13-cRA/d given to patients with treated squamous cell carcinoma of the oral cavity, pharynx or larynx resulted in fewer second primary cancers. However, there was no benefit in overall survival or recurrence rate of the initial cancers, and 33% of the patient could not complete the 12-month protocol because of the side effects. With longer follow-up, the investigators found that after 3 years there was no reduction in the rate of second primary tumors among the 13-cRA-treated group.

The role of 13-cRA in the prevention of second primary oropharyngeal cancers is questionable because the results do not show a significant benefit, and some of these patients are already suffering from oral complaints due to the therapy for their initial carcinoma and may have difficulty tolerating the 13-cRA. Strongly encouraging patients to stop their use of tobacco and alcohol products and providing counseling seems to be a more effective way of reducing second primary oropharyngeal cancer.
Prescribing information: The range of 0.5 to 1 mg/kg/d of 13-cRA as a starting dose is used for the treatment of premalignant oral lesions. 13-cRA is supplied in 10, 20 and 40 mg capsules. Before prescribing 13-cRA, the possible side effects must be explained carefully to the patient. In addition, it is necessary to confirm unequivocally that the patient is not pregnant and, if she is still capable of reproduction, there must be medically acceptable program of contraception for 1 month before starting 13-cRA, while taking the 13-cRA, and for 1 month after discontinuation because of the probability of birth defects.

Beta-carotene

Beta-carotene is the most active carotenoid, and its only apparent role is as a precursor for vitamin A because it is difficult to identify specific clinical problems in patients with diminished beta-carotene intake. Beta-carotene is found in vegetables and fruits, such as carrots, spinach, sweet potatoes. In general, the deeper color of the vegetable or fruit, the greater the beta-carotene content. Some studies have shown that the higher the intake of beta-carotene, the lower the risk for developing oropharyngeal cancer. However, this finding is not consistent, and one study showed no benefit.

USE WITH ORAL LESIONS

Studies have shown clinical improvement in 15 to 71% of the patients who received beta-carotene supplements for the treatment of oral leukoplakia. Although somewhat promising, this rate is not remarkably better than the spontaneous resolution rate that has been reported in a large group of patients with oral leukoplakia and among patients who discontinue their use of tobacco and alcohol products.

PREVENTION OF A SECOND PRIMARY OROPHARYNGEAL CANCER

One study of 380 cases of cancer of the oral cavity, pharynx or larynx found that an increased dietary intake of beta-carotene was associated with decreased risk for developing a second primary cancer. However, it is not known if the beta-carotene was the factor responsible or if it was something else in the lifestyle of patients who eat more fruits and vegetables.

Ascorbic Acid

Popularly known as vitamin C, ascorbic acid is present in citrus fruits and leafy vegetables. The RDA for adults ranges from 60 mg/d (nonsmokers) to 100 mg/d (smokers). An increased cancer risk of various anatomic sites has been associated with low ascorbic acid dietary intake and serum levels. Ascorbic acid has not been used as the sole agent in the treatment of oral leukoplakia but was used in one study that combined it with beta-carotene and alpha-tocopherol (AT). This study found clinical improvement in 55.7% of 79 patients with oral leukoplakia.

Alpha-tocopherol

The most common and most active form of vitamin E is AT, which is found in margarine, plant oils and green leafy vegetables. AT is stored in the liver and adipose tissue and is excreted primarily in the feces. The role of AT in the prevention of cancer is unknown, but one study showed that vitamin E supplements were associated with a diminished risk for oral and pharyngeal cancer. Hamster studies also have shown that AT may help in the regression of artificially induced carcinomas of the buccal pouch.

USES WITH ORAL LESIONS

Benner et al found that almost half of their patients with oral leukoplakia showed clinical improvement after administering 800 IU of AT/day for 24 weeks. Larger studies with long-term follow-up are required to assess the potential of AT in treating oral leukoplakia. The principal advantage of AT is the lack of toxicity.

RECOMMENDED DOSE OF ANTIOXIDANT VITAMINS

<table>
<thead>
<tr>
<th>Antioxidant vitamin</th>
<th>Recommended daily allowance</th>
<th>Doses used in the treatment of oral lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>5,000 IU</td>
<td>0.5-1 mg/kg/d of 13-cis-retinoic acid</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>75 mg</td>
<td>1,000 mg/d</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10 mg</td>
<td>536.9 mg/d</td>
</tr>
</tbody>
</table>

RISKS OF ANTIOXIDANT SUPPLEMENTS

The idea of taking supplements to compensate for poor diet is attractive and indeed, vitamin supplements are common place. Could this possibly present a risk to the person who takes the supplements? Among a large group of pregnant women, it was discovered that 1.4% of them averaged more than 10,000 IU of vitamin A per day from supplements, and it was estimated that one of 57 babies born to this group of women would have a birth defect attributable to their vitamin A intake.

The possibility of developing squamous cell carcinoma is a concern when using antioxidants to treat patients with premalignant oral lesions and should be expected to occur in some patients. In a clinical trial of 79 patients who were supplemented with beta-carotene, ascorbic acid and AT,
7 (8.9%) developed squamous cell carcinoma during the 9-month supplementation or within 1 year of discontinuation. A study from MD Anderson Cancer Centre reported that 17 of 70 (24.3%) patients with premalignant oral mucosal lesions developed either in situ or invasive carcinoma within the median follow-up time of 66 months after supplementation began with 13-cRA or beta-carotene or both. Of their patients, 86% were diagnosed histologically as having hyperplasia or mild epithelial dysplasia at the beginning of the study.

Therefore, a relatively high percentage of supplemented patients experienced a malignant transformation despite favorable baseline histologic diagnosis. The similar rate of cancer development in the two supplementation groups indicates that neither beta-carotene nor 13-cRA was superior in preventing a malignant change in oral leukoplakia and that there might not even be a long-term advantage when compared with group of patients with epithelial dysplasia who were not treated.

Is it possible that antioxidant supplements promote carcinogenesis instead of retarding it? There is in vitro evidence that ascorbic acid acts as a pro-oxidant by increasing oxidative damage. Interestingly, this was also noted in a study that found that artificially induced carcinogenesis in the buccal pouch of hamsters was enhanced by ascorbic acid. Patients had a rapid transition from moderate epithelial dysplasia to squamous cell carcinoma. This malignant transformation may have occurred without the use of antioxidants, but we should be worry of this possibility. Patients with premalignant oral mucosal lesions that are being treated with antioxidants must receive careful and frequent clinical monitoring, including incisional biopsies, in order to diagnose malignant change at the earliest possible time.23-26

CONCLUSION

Surgery remains the treatment of choice for premalignant oral lesions, but is there a role for antioxidants in the treatment of oral lesions? There was initial excitement regarding the use of antioxidants in the treatment of premalignant oral lesions because of the in vitro, animal, and epidemiologic studies that reported an association between low levels of antioxidants and cancer throughout the body. Unfortunately, antioxidants are not the ‘magic bullet’ for the treatment of premalignant oral mucosal lesions or the prevention of second primary malignancies. However, there is a role for antioxidants, if used judiciously in selected cases that can be monitored carefully. An important principle is that the treatment should not be more harmful than the damage that the lesion can cause.

REFERENCES


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