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Interventions in Management of Oral Leukoplakia: A literature Review

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Abstract

Oral leukoplakia is the most common potentially malignant disorder affecting oral cavity. Various surgical and non-surgical treatments have been reported, but currently there is no universal consensus on the most appropriate one and on the duration or interval of follow-up of patients with this condition. Management of oral leukoplakia should begin with elimination of risk factors such as tobacco abuse, alcohol abuse, and superimposed candida infection over the lesion etc. Conservative treatment includes use of chemopreventive agents such as vitamins, fenretinide, carotenoids bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcuma etc. The aim of this review is to present recent advances in medicinal management of oral leukoplakia.

Keywords: Medicinal, oral leukoplakia, oral cavity.

Introduction

Oral leukoplakia (OL) is a premalignant lesion described as "a predominant white lesion of the oral mucosa which cannot be defined as any other known lesion".[1] According to Warnakulasuriya et al. the new concept of OL shall acknowledge white lesions with questionable risk of being an OL, being excluded any other pathologies or known disorders which do not present potential malignant risk such as candidiasis, lupus erythematosus, lichen planus, hairy leukoplakia, frictional keratosis, nicotinic stomatitis, and leukoedema.[2]

Oral leukoplakia's etiopathogenesis encompasses two broad categories, as follows: Oral leukoplakia of unknown etiology or idiophatic and Oral leukoplakia associated with tobacco use.[3,4] Oral leukoplakia is more often found among older and elderly men, and its prevalence increases with age advancement. It has been estimated that less than 1% of the affected men are younger than 30 years old and that the prevalence increases to 8% in male patients older than 70 years old and to 2% in female patients of 70 years or more. OL's histopathologic aspects may vary from epithelium atrophy to hyperplasia, which can be associated with varying degrees of epithelial dysplasia.[4,5] Oral leukoplakia located on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, in other areas, they may be considered as of low malignancy risk.[5,6] Oral leukoplakia has an annual malignant transformation rate of 0.1% to 17%.7 Some factors may contribute to increase the chance of the OL becoming malignant, which are as follows:[4,6]

(1). Gender: female patients tend to present a higher risk of developing the malignant form.

(2). A long-time Oral leukoplakia lesion which may be resistant to the treatments and what persist for long time may have worse prognosis than recent.

(3). Oral leukoplakia in sites of high risk of malignant transformation, sites such as lesions in the floor of mouth, ventrolateral tongue and soft palate.

(4). Oral leukoplakia among nonsmokers (idiopathic): nonsmokers with OL have an increased rate of malignant transformation in relation to OL in smokers.

(5). Nonhomogenous Oral leukoplakia-type, they may have a mixed colour of white and red alterations, and an exophytic, papillary, or verrucous aspect; regardless of treatment. These lesions exhibit a high recurrence rate and often eventually transformation to squamous cell carcinoma.

(6). Epithelial dysplasia: Oral leukoplakia with moderate and severe dysplastic lesions had a significantly higher risk of developing a squamous cell carcinoma than Oral leukoplakia without epithelial dysplasia or with mild epithelial dysplasia.[7]

In order to conduct treatment for Oral leukoplakia, the degree of epithelial dysplasia should be assessed. Oral leukoplakia presenting low to moderate

malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation.[4] Oral leukoplakia surgical treatment may be performed either through conventional surgery, electro cauterization, laser ablation, or cryosurgery.[4,5,8] Recurrence of Oral leukoplakia after surgical treatment has been reported in 10%–35% of cases.[9] Nonsurgical treatment may also be considered for the management of Oral leukoplakia.[10] This modality offers minimal adverse effects to patients, especially for patients with widespread Oral leukoplakia that involves a large area of the oral mucosa or patients with medical problems and, consequently, high surgical risks. Additionally, potential advantages of the nonsurgical treatment of Oral leukoplakia include easy application that does not require treatment at a medical center and relative low cost.

Various treatment modalities for the treatment of oral leukoplakia:-

Carotenoids

a. Beta-carotene

The use of beta-carotene has been recommended in order to prevent Oral leukoplakia and possibly oral cancer.[11] The potential benefits and protective effects against cancer are possibly related to its antioxidizing action. This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals. According to Liede et al, diet supplemented with beta-carotene can prevent changes in the oral mucosa, especially in smoker patients, who present low serum levels of vitamin C and beta-carotene when compared to non-smokers.[12] It has also been shown that beta-carotene has a better therapeutic clinic response in the prevention of Oral leukoplakia lesions, and in smoker patients than in the non-smoker ones.[13]

b. Lycopene

Lycopene is a carotenoid without provitamin A action. Lycopene is considered one of most efficient biological antioxidizing agent.[14] There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases. Lycopene is believed to modify intercellular exchange junctions, and so effective in potentially malignant disorders. [14]

Lycopene (from the New Latin word Lycopersicum for the name of tomato species) is a bright red carotene and carotenoid pigment. It is a phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, red bell peppers, watermelons, and papayas (but not strawberries or cherries). Orly Livny, et al, studied the role of lycopene and β carotene and suggested that lycopene strongly and dose dependently inhibited proliferation of KB 1 human oral tumor cells. B Carotene was a far less effective growth inhibitor. [15]

Vitamins

a. Vitamin A

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A.[16,17] The most biologically, naturally occurring retinoid is vitamin-A. Vitamin A, also known as retinol, is an alcohol that can be converted into an aldehyde (retinal) or retinoic acid.[18] Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins.[19] Vitamin A is required in the normal pathway of epithelial cell differentiation and production of keratin.[18]An association between vitamin A deficiency and the enhanced susceptibility to carcinogenesis was reported with an increased risk for developing different epithelial carcinomas.[18]Several other processes are influenced by retinoids, such as the expression of growth factors and kinases, oncogenesis, apoptosis, production of collagen matrix, immune and inflammatory responses, cell differentiation, embryonic morphogenesis and carcinogenesis.[19]

A study conducted by Olson et al reported that complete remission of Oral leukoplakia was observed in 57% of patients who received vitamin A about 2,00,000 IU. [20], In another study patients with Oral leukoplakia treated by beta-carotene (180 mg/week) plus vitamin A (100.000 IU/week) showed significant results. During the trial period, all patients continued to chew tobacco-containing betel quids.[21]

b. Fenretinide

Fenretinide (4-HPR) or N-(4-hydroxyphenyl) retinamide is a vitamin. This retinoid shows a preferential accumulation in breast instead of liver, is effective in the inhibition of chemically induced mammary carcinoma in rats, and has proven to be less toxic than many other vitamin A analogues.[22] A characteristic feature of 4-HPR is its ability to inhibit cell growth through the induction of apoptosis

with mechanisms that may be both receptor-dependent and receptor-independent. Chemo preventive efficacy of fenretinide has been investigated in clinical trials targeted at different organs with a systemic use of 4-HPR with 200 mg/day for 3 months. [19]

c. Acitretin

Acitretin is a synthetic aromatic retinoid that is considered as an option in the treatment of severe keratinisation disorders. Acitretin is a free acid of etretinate and its main metabolite, therapeutic activity and side effects, including teratogenecity, are identical to those of etretinate. These side effects make a topical form of actitretin with no reduced systemic adverse effects desirable.[19]

d. α-Tocoferol (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 anti-tumor proliferation capacity as well as function as a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids.[23,24] It is found in plant oil, margarine, and green leaves. Benner et al., in 1993 suggested 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. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women.[23]

e. L-Ascorbic Acid (L-AA)/ Vitamin C

L-AA has antioxidizing properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. Vitamin C can be found in citrus fruits such as kiwi, strawberries, papaya, mango etc.[23] The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes.[23] L-AA toxicity does not occur, since vitamin is water-soluble. The ability of L-AA to maintain oral mucosa integrity is very little documented. [23]

f. Bleomycin

Bleomycin with iontophoresis has been studied in the treatment of Oral leukoplakia and papillomas of the head and neck region.[25] This method of application was not effective for malignant lesions, but was effective at removing leukoplakia of the oral mucosa. A single case of the complete resolution of hyperkeratotic leukoplakia with atypia using local injections of 5 mg of bleomycin weekly in eight treatments has been reported. [25]

Spirulina

The blue green microalgae Spirulina, used in daily diets by natives of Africa and America, have been found to be a rich natural source of proteins, carotenoids, and other micronutrients. Experimental studies in animal models have demonstrated an inhibitory effect of Spirulina algae on oral carcinogenesis.[25] Mathew et al., evaluated the chemo preventive activity of Spirulina fusiformis (1 g/day for 12 months) in reversing Oral leukoplakia in pan tobacco chewers in Kerala, India. Complete regression was seen in 16 of 28 (57%) subjects with homogeneous leukoplakia, 2 of 8 with erythroplakia, 2 of 4 with verrucous leukoplakia, and 0 of 4 with ulcerated and nodular lesions. [25]

Celecoxib

The epithelial growth factor receptor (EGFR) is expressed in a wide variety of malignant tumors including head and neck, colon, pancreatic, non-small cell lung, breast, kidney, ovarian, bladder carcinomas and gliomas. The incidence of EGFR expression in head and neck squamous cell carcinoma (HNSCC) is over 90%, suggesting that EGFR inhibition may be effective in HNSCC. [26] A broad range of laboratory investigations, animal models, and epidemiological studies provide evidence that inhibition of cyclooxygenase-2 (COX-2) pathways may contribute to cancer treatment in general and HNSCC in particular. In HNSCC, COX-2 is expressed in both tumor tissue and adjacent epithelium, with increased expression in invasive carcinoma compared to normal epithelium. COX-2 inhibition has been shown to result in cell growth inhibition in HNSCC cell lines.[26] COX-2 levels increased progressively throughout all stages of carcinogenesis.

Green tea

Green tea and its major polyphenols constituents, tea catechins, have been shown to have many health benefits including cancer prevention. Tea catechins and tea catechin metabolites/catabolites are

bioavailable in the systemic circulation after oral intake of green tea or green tea catechins. Tea pigments are the oxidized product of 40% green tea polyphones and are composed primarily of thea flavins and thearubigins. Applying the tea extracts directly to the lesions may help improve the local concentrations of the active constituents.[27]A limited number of chemoprevention trials of green tea or green tea catching have been conducted to date and have observed potential preventive activity for oral, prostate, and colorectal cancer.

Cur cumin

Cur cumin has been used for thousands of years in traditional Indian medicine.[27] Cur cumin reportedly possesses several pharmacological properties, including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo-sensitizing, radio-sensitizing, and wound healing activities. It is known to suppress tumor initiation, promotion and metastasis in experimental models, and it can also act as an anti-proliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micro nucleation. [27]

Flavinoids

Flavonoids are a group of plant derived phenolic compounds that have been identified to have antioxidant property to reduce the risk of development of chronic diseases. Flavonoids have an additive effect to the endogenous scavenging systems [28]. They have different functions in the antioxidant system like:

a. Direct Radical Scavenging: Flavonoids stabilize the reactive oxygen species by reacting with the reactive compound of the radical thereby producing a less reactive radical. Few flavonoids directly scavenge superoxide while others scavenge peroxynitrites.[28]
b. Nitric Oxide: Nitric oxide produced by macrophages reacts with free radicals producing peroxynitrite which can react with low density lipoproteins thereby producing irreversible injury to the cell membrane. Flavonoids scavenge nitric oxide as well as peroxynitrite thus reducing the amount of oxidative damage.[29]
c. Xanthenes Oxidize: Xanthenes dehydrogenize, an enzyme present under physiologic conditions is changed to xanthenes oxidize during ischemic conditions. During reperfusion, xanthenes oxidize reacts with molecular oxygen thereby producing superoxide free radicals.[28]
d. Leukocyte Immobilization: During ischemia and inflammation, leukocytes which are freely moving along the endothelial wall are acted upon by endothelium derived mediators and complement factors and adhere to the endothelial wall and stimulate degranulation of neutrophils.[29]

5% imiquimod

Imiquimod belongs to the family of synthetic small nucleotide-like molecules of imidazoquinolinamines. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base. It is an immune response modifier with potent antiviral and antitumor effects, which are mediated by Toll-like receptors (TLR7 and TLR8).[29] Topical imiquimod cream 5% is effective to treat actinic keratoses, superficial basal cell carcinoma, and an genital warts. Topical imiquimod is especially recommended to treat large clinically asymptomatic fields containing tumor cells “field concretization,” which is prevalent in oral potentially malignant lesions. [29]

Proton Pump Inhibitors

The oral mucosa is thin and susceptible to various irritants like the laryngeal mucosa and hence the oral leukoplakia has correlating mechanisms with laryngeal leukoplakia. The proton pump inhibitor has been used in the treatment of laryngeal leukoplakia and proven to improve laryngeal mucosal damage.[30] The Proton pump inhibitor aids in irreversible blockage of the hydrogen/potassium adenosine tri phosphates enzyme system (H+/K + ATPase) of the gastric parietal cells and inhibits acid secretion. Proton pump inhibitors have the ability to chemosensitize different cells through a normalization of extracellular pH hydrogen ion concentration. [30]

Conclusion

Oral Leukoplakia is the most common premalignant or potentially malignant lesion of the oral mucosa. The cessation of tobacco habits, being the most common known aetiological factor of oral leukoplakia. Several clinical trials have investigated the treatment of Oral Leukoplakia with use of supplements. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve Oral Leukoplakia. The small number of patients, the lack of controls, the lack of widely accepted criteria for classifying Oral Leukoplakia, the variability in nonsurgical treatment protocols, and differences in histopathologic evaluation difficult the interpretation

of data of the few randomized clinical trials in nonsurgical treatment of Oral Leukoplakia. At this time, randomized controlled trials for nonsurgical treatment of OL demonstrate no evidence of effective treatment in preventing malignant transformation and recurrence. It reinforces that after clinical resolution, Oral Leukoplakia should be regularly followed.

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