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Insight of Various Medical Management of Oral Leukoplakia

T. MANIGANDAN* and V.T. HEMALATHA

Department of Oral Medicine and Radiology, Sree Balaji Dental College and Hospital, Bharath University, Chennai, India
*Corresponding author E-mail: manident@yahoo.com

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ABSTRACT

Oral leukoplakia [OL] is a relatively common oral lesion that which can undergoes malignant transformation. The aim of this review was to assess the effectiveness of treatments for leukoplakia. A medline search from 1983 to 2014 was conducted. The topical or systemic nonsurgical treatments or combination of both was reviewed.

Key words: Oral leukoplakia, premalignant lesion, beta carotene, retinoids, green tea, spirulina, lycopene, photodynamic therapy, acitretin, Vitamin A, C & E, Fenretinide, Bleomycin, celecoxib.

INTRODUCTION

OL is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion[1] Such a definition, also adopted by the World Health Organization, is the result of the effort of an international group of experts who met in Uppsala in 1994 to review leukoplakia definitions and classifications on the basis of previously published work[2,3]

OL prevalence in the general population varies from less than 1 to more than 5 percent.[3-7].

Clinical variants

There are two clinical variants: 1) Homogeneous leukoplakia, a lesion of uniform flat appearance that may exhibit superficial irregularities, but with consistent texture throughout; and 2) non-homogeneous leukoplakia, a predominantly white or white and red lesion (erythroleukoplakia) with an irregular texture that may present as a flat, nodular, or exophytic lesion.

Management of leukoplakia

Leukoplakia is a lesion which is mostly asymptomatic it has got a tendency to change into squamous cell carcinoma. The rate of malignant transformation varies from almost 0 percent to about 20 percent in age group one to thirty years.[8-10] Toludine blue plays a vital role in detection of early dysplastic changes in precancerous lesions. It is the useful chairside diagnostic test which can be performed within 5 min time with high sensitivity of 100% and specificity of 92%.[11]

A medline search from 1983 to 2014 was conducted. The aim was to assess the evidence of efficacy for treatments for leukoplakia.

Various treatment modalities for the treatment of leukoplakia.

Carotenoids

Beta-carotene

The use of beta-carotene has been recommended in order to prevent OL and possibly oral cancer.[12-14] The potential benefits and protective effects against cancer are possibly related to its antioxidizing action.[15-17] 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.[17]According to Liede et al.[15], a 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. It has also been shown that beta-carotene has a better therapeutic clinic response in the prevention of OL lesions, and in smoker patients than in the non-smoker ones.[18]

Lycopene

Lycopene is a carotenoid without provitamin A action. Lycopene is considered one of most efficient biological antioxidizing agent.[19] 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[20] Lycopene is believed to modify intercellular exchange junctions, and so effective in potentially malignant disorders. [19]

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). Although lycopene is chemically a carotene, it has no vitamin A activity. Orly Livny, *et al.* studied the role of lycopene and â carotene and found that lycopene strongly and dose dependently inhibited proliferation of KB 1 human oral tumor cells. â Carotene was a far less effective growth inhibitor.[21] The results of their study further supported the hypothesis that carotenoids, in general, and lycopene, in particular, may be effective anticarcinogenic agents in oral carcinogenesis.

Further, numerous other potentially beneficial compounds are present in tomatoes and their complex interactions among multiple components may contribute to the anticancer properties of tomatoes[22-23].

Vitamins

Vitamin A

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Retinoic acid is obtained from carotene and animal products such as meat, milk, and eggs, which, while in the intestine, are converted, respectively, into retinal and retinol[24-27]. Supplementation with retinoids for OL treatment began in the 1960s. However, this treatment was not widely accepted due to its side effects—hypervitaminosis, toxicity, teratogenic effects, and alterations in various organic systems[28].

13-cRA is the retinoid recommended for OL treatment. The use of 13-cRA has been shown to be effective in resolving OL[25,26]. However, the high recurrence rates after short periods of discontinuance, together with its side effects, are limiting factors[25, 26,28].

A study conducted by Olson et al reported that complete remission of OL was observed in 57% of patients who received vitamin A about 2,00,000 IU. [29] In an other study patients with OL 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[30].

The systemic use of retinoids may lead to severe adverse effects, especially in individuals who need high doses of medication or long-term treat-ment. The toxicity seems to be dose-dependent and recurrences are common after the discontinuation of its use[31,32,35]. Therefore, a close follow-up of these patients is mandatory. On the other hand, the topical administration of retinoids allows the application of higher concentrations of the drug directly on the lesion but with less adverse effects [31,33].

One study reported that all 26 patients using topical 0.05% tretinoin gel four times a day for 3.5 years showed signs of clinical improvement. However, 27% showed total remission and 40% of these patients had recurrence of the disease after the discontinuation of the treatment[35]

In one study, patients received a fixed dose of 13-cRA (10 mg/day) plus an escalating dose (beginning at 800 IU/day, until 2000 IU/day) for 4 months. Seventy-one percent of OL patients had complete clinical responses.[36]

Fenretinide

Fenretinide (4-HPR) or N-(4-

hydroxyphenyl) retinamide is a vitamin A analogue that was synthesized in the United States during the late 1960s. This retinoid shows a preferential accumulation in breast instead of liver[37], is effective in the inhibition of chemically induced mammary carcinoma in rats[38], and has proven to be less toxic than many other vitamin A analogues[38,39]. 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. Chemopreventive efficacy of fenretinide has been investigated in clinical trials targeted at different organs [40-42]. A phase II trial of 4-HPR (200 mg/day) was carried out for 3 months in OL patients who had not responded ("de novo" resistance) or who had responded and then relapsed (acquired resistance) to the previous treatment with natural retinoids. Of 35 patients with retinoid-resistant OL, no patient had complete responses and 12 (34.3%) had partial responses to 4-HPR. Nine patients had clinical responses within 9 months of stopping 4-HPR. Toxicity was minimal and compliance was excellent [43]. Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of 12 patients.

β-Tocoferol (Vitamin E)

β-Tocoferol (AT) is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves[44–47]. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women[48]. Its absorption rate is reduced when consumption exceeds 30mg/day[49]. β- Tocoferol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation[45,46,50,51]. Supplementation with AT led to a significant rise in the concentration of this antioxidant in the plasma.

Benner *et al*.,[52] evaluated the toxicity and efficacy of AT in 43 patients with OL in use of 400 IU twice daily for 24 weeks. Follow-up was performed at 6, 12, and 24 weeks after the beginning of treatment to assess toxicity, clinical response, and serum AT levels. It was observed that 10 patients (23%) had complete clinical remission of lesion and 10 (23%) had a partial clinical response. Nine (21%) had histologic responses (complete reversal of dysplasia to normal epithelium). Mean serum AT levels were 16.1 µg/mL at baseline and increased to 34.29 *µ*g/mL after 24 weeks of treatment.

L-Ascorbic Acid (Vitamin C)

L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrous fruits such as kiwi, strawberries, papaya, and mango. Recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults[53]. 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[54].

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[55]. L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day[56]. There are no studies regarding the efficacy of the use of L-AA alone for OL treatment.

Bleomycin

Bleomycin with iontophoresis has been studied in the treatment of leukoplakia and papillomas of the head and neck region.[57] 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[58]. Six patients with OL were treated with a daily topical application of bleomycin in dimethylsulphoxide (DMSO) with 12 to 15 application[59]. Repeat biopsies from 10 to 84 days after therapy demonstrated reduction in keratinization and dysplasia. The authors assumed total absorption of all topically applied bleomycin, yielding a maximum 15-mg systemic dose. This is well below the doses used in the usual systemic therapy.

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 etabolites/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 polyphenols and are composed primarily of theaflavins and thearubigins. Applying the tea extracts directly to the lesions may help improve the local concentrations of the active constituents.

A limited number of chemoprevention trials of green tea or green tea catechins have been conducted to date and have observed potential preventive activity for oral, prostate, and colorectal cancer. Emerging data from multiple ongoing intervention trials will further contribute to defining the cancer preventive activity of green tea or green tea catechins[60].

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.

Mathew, et al. (1995) evaluated the chemopreventive activity of Spirulina fusiformis (1 g/day for 12 months) in reversing OL in pan tobacco chewers in Kerala, India. They observed complete regression of lesions in 20 of 44 (45%) subjects supplemented with S. fusiformis, as opposed to 3 of 43 (7%) in the subjects on placebo ($P < 0.0001$). When stratified by the type of leukoplakia, the response was more pronounced in homogeneous lesions: 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[61].

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 (62-64). 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[65-67].

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[68-70] and HNSCC in particular[71,72]. 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[73].

COX-2 levels increased progressively throughout all stages of carcinogenesis. This may reflect a role for COX-2 in this process, further supporting the rationale for COX-2 inhibition as a valid strategy for cancer chemoprevention.

Acitretin

Acitretin is a synthetic aromatic retinoid that is considered as a 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.

In a study conducted by GM Gaeta et a[74] , they concluded that 71% of patient showed clinical remission or marked improvement. The mucoadhesive tablet of topical acitretin are efficacious in the treatment of OL without systemic side effects.

Photodynamic Therapy

Photodynamic therapy (PDT) is a noninvasive method for the treatment of premalignant lesions and head and neck cancers[75]. The principle of PDT is a nonthermal photochemical reaction, which requires the simultaneous presence of a photosensitising drug (photosensitiser), oxygen, and visible light. After a period to allow the photosensitiser to collect in the target tissue, the photosensitiser is activated by

exposure to low-power visible light of a drug-specific wavelength. Mainly, the light source consists of a portable diode laser and the light is transmitted via laser fibres to or into the tumour. Illumination of the tumour by light at the activating wavelength results in the destruction of cells by a nonfree radical oxidative process. These reactive oxygen species may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids. PDT is a cold photochemical reaction, and the photosensitizing agents are of inherently low systemic toxicity. PDT damage heals mainly by regeneration rather than scarring. Due to the organ preserving principle of PDT, important structures are maintained with good functional and cosmetic outcome[76,77].

Four photosensitisers have been approved so far: (1) photofrin has been approved in many countries for the treatment of oesophagus cancer and lung cancer; (2) 5-Aminolaevulinic acid (ALA) was also approved in several countries for the treatment of skin cancer; (3) verteporfin for the treatment of macular degeneration (4) foscan is the only photosensitiser that has been approved for the treatment of advanced squamous cell carcinoma of the head and neck in Europe in the year 2001. Only for very superficial skin lesions or premalignant lesions of the oral mucosa, the ALA can be applied topically. For all other indications intravenous application is mandatory[78].

Chen *et al.*[79] treated 24 patients with OL using 20% ALA-PDT, once a week; another 24 patients used 20% ALA-PDT twice a week. In the latter group, 8 completely responded to the treatment, 16 partially responded, and 9 did not. All patients from the twice-a-week group responded significantly better than those treated only once a week.

CONCLUSION

Dentist and general practitioner pay an essential role in the early diagnosis of leukoplakia which is usually asymptomatic and removal of possible factors involved in its etiology such as smoking is necessary in reducing the rate of malignant transformation. Though many trials have been done to find new treatment modalities for leukoplakia there has been no satisfactory treatment for leukoplakia so far. It can be concluded that, although some treatments may be effective in healing OL, they do not seem to be able to prevent relapses and malignant change. For this reason, OLs need to be regularly followed up by the clinician, regardless of their response to topical or systemic treatment, including clinical resolution and instructed to avoid the major risk factors of oral epithelial dysplasia, especially tobacco usage and alcohol consumption.

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