Non-Surgical Management of Oral Leukoplakia

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Abstract

The aim of this paper was to assess the nonsurgical treatment of oral leukoplakia (OL). The topical or systemic nonsurgical treatments or combination of both was reviewed. The primary outcomes of interest were clinical resolution, malignant transformation, follow-up, and recurrence of OL.

Introduction

“Leukoplakia is a whitish patch or plaque that cannot be characterized, clinically or pathologically, as any other disease and it is not associated with any physical or clinical causative agent except the use of tobacco”.1

Establishing the clinical diagnosis of leukoplakia, followed by histopathologic analysis, leads to consideration of the appropriate clinical management which should be designed according to the anticipated clinical or biologic behavior. Balancing the lesional qualities with treatment modality and associated morbidity becomes the major clinical decision. With such considerations in mind, a wide choice of treatments has been used, ranging from those which are locally directed to others which are systemic. In the absence of histologically demonstrated dysplastic changes, careful and routine follow-up observations of leukoplakia may be appropriate in conjunction with elimination of any risk-associated behavior or habits. In order to conduct treatment for OL, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. However, OL 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.2

Low risk leukoplakia: Leukoplakias having no dysplastic features or having mild dysplasia associated with following features is considered as low risk leukoplakias.

a. Site not in high risk area
b. Size less than 200mm
c. Homogenous clinical form

Their treatment protocol requires regular follow up along with usage of topical or oral...
medications like Beta carotene, Lycopene and others. If no benefit is attained then non surgical ablative therapies like Cryotherapy or CO₂ laser are used. If the resolution of the lesion has occurred then only regular follow up is required. While if the lesion does not resolve then the treatment is repeated, but on repetition of negative response surgical decortications is advised. The histological analysis of the specimen is done if the specimen show areas of squamous cell carcinoma then radical excision are planned with or without radiotherapy or chemotherapy. While if the areas of squamous cell carcinoma are absent then only regular follow up is done every 3 months for the first year and subsequent follow up is done within 6-12 months. ³

**High risk leukoplakia:** A leukoplakia is considered to be a high risk if it shows mild dysplasia associated with following features:

- Site in high risk area
- Size greater than 200mm
- Non homogenous clinical form

Or it displays moderate to severe dysplasia. In such cases surgical decortications is advised followed by histopathological analysis of the specimen. If the specimen show areas of squamous cell carcinoma then radical excision are planned with or without radiotherapy or chemotherapy. While if the areas of squamous cell carcinoma are absent then only regular follow up is done every 3 months for the first year and subsequent follow up is done within 6-12 months. ³

**Treatment Modalities**

**I. Behaviour Modification:** Cancer appears more frequently in persons who do not stop alcohol or tobacco use. Nevertheless, leukoplakias in nonsmokers appear to have a higher risk of progression to cancer. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped. Leukoplakias induced by smokeless tobacco may resolve if the habit is stopped. Some candidal leukoplakias respond, at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress. In view of the evidence linking alcohol and tobacco, betel, and diet, to the development of potentially malignant and malignant oral epithelial lesions, it would seem reasonable therefore, that habits such as the use of tobacco and alcohol should be actively discouraged, and a good diet and oral hygiene encouraged. Unfortunately, only a few patients change their habits. The effects of dietary or oral hygiene modification on leukoplakia appear still not have been studied. ⁴

The treatment of leukoplakia is done after consideration of their risk potential i.e. low risk leukoplakia and high risk leukoplakia. ³

**II) Nonsurgical Treatment Modalities:** Nonsurgical treatment may also be considered for the management of OL. This modality offers minimal adverse effects to patients, especially for patients with widespread OL 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 OL include easy application that does not require treatment at a medical center and relative low cost. ⁵

1. **Carotenoids:** The carotenoids are a group of extremely hydrophobic molecules with little or no solubility in water. ⁶

   **A. Beta-Carotene:** Beta-carotene is a vitamin A precursor. ⁶,⁷,⁸

   **Source:** Beta-carotene is a carotenoid commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. ⁶

   The use of beta-carotene has been recommended in order to prevent oral leukoplakia and possibly oral cancer. ⁹ 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. ¹⁰

   According to Liede et al., 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 nonsmokers.

   It has also been shown that beta-carotene has a better therapeutic clinic response in the
prevention of oral leukoplakic lesions in smoker patients than in the nonsmoker ones.11

**Side effects:** The only known effect of excessive beta-carotene intake is a state in which the skin becomes strongly yellowish, the so-called carotenodermia, which disappears in a few weeks after the reduction of consumption.5

While some authors have demonstrated the absence of side effects in patients that have received beta-carotene treatment, in other studies, the supplement diet based on beta-carotene cause headaches and muscle pain in some of the patients.5

In another study, 23 patients with OL were treated with beta-carotene, in oral doses of 90mg/day, for three cycles of 3 months each. Of 18 patients who completed the study, 6 (33.3%) showed complete clinical response. No significant clinical signs of toxicity were detected in any of the patients.5

**B. Lycopene:**12 Lycopene is a carotenoid without provitamin A action. This is a fat-soluble red pigment found in some fruit and vegetables.

**Source:** The greatest known source of lycopene is tomatoes, which are widely employed in cooking.

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 has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidant agent. Due to this property, studies have been enthusiastically conducted with lycopene, in order to find out whether or not it could be an alternative to protect patients against the damaging effects of free radicals.

In addition to its antioxidant property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism. In vitro experiments have shown the inhibition of the process of human neoplastic cellular growth by lycopene, since this protein interferes in growth factor receptor signaling and, thus, in cellular cycle progression, as previously demonstrated for neoplastic cells from the prostate gland.

Consumed carotenoids are incorporated in lipidic micelles and are absorbed by enteric mucosa through passive diffusion and distributed to the organs by the plasmatic lipoproteins. Lycopene release from the food matrix, presence of fat in the diet, and heat-induced isomerization from trans to cis mode are some factors influencing lycopene absorption and biodisposibility. Lycopene is better absorbed in oil resin capsules and in tomato juice than in the form of raw tomatoes.

The serum levels of lycopene and beta-carotene, among the 38 men suffering from OL, were significantly lower than those of the control group (P < .005). Authors suggested that improvement of micronutrient levels of beta-carotene and lycopene in Japanese males with a high frequency of smoking habit may protect against the relative risk of OL in this population.

**Side effects:** No systemic significant toxic effects of lycopene have been observed and there is no evidence of side effects from the treatment with lycopene. Lycopene is a promising candidate in reducing cancer and chronic diseases in human beings; however, further research is needed to clarify its potential function in human health, according to the following criteria.

(1) Factors influencing the uptake of lycopene in the diet, including the way it interacts with other carotenoids.

(2) Human metabolism and the possible function of the metabolites and cis-trans isomers.

(3) Mechanisms of the direct or indirect modulation of cancer.

(4) Studies based on evidences of treatment in human beings.

(5) Mechanisms of lycopene deposition in human tissues.

(6) Lycopene effects in the immunological system.

**2. Vitamins:**

**A. L-Ascorbic Acid:** L-ascorbic acid (L-AA), the so-called vitamin C.

**Source:** Citrus fruits such as kiwi, strawberries, papaya, and mango.
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.

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.

L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day.

The ability of L-AA to maintain oral mucosa integrity is very little documented. One study examined the presence of oral mucosal lesions in subjects with low L-AA levels in plasma, compared to controls. Subjects with low plasma L-AA levels ≤25 μmol/l (n=106) formed the study group and individuals with normal L-AA levels (≥50 μmol/l) (n = 103) formed the control group. Oral mucosal lesions in all subjects were defined clinically as petechias, OL, and lichenoid lesions. There was a statistically significant difference between the groups only for OL, where the prevalence of OL was higher when smoking was combined with L-AA deficiency.

In another study, 24 OL patients were treated with an association of beta-carotene, vitamin E, and L-AA, and an increase was observed in the reversion of oral mucosa dysplasia. In 97.5% of patients, dysplasias were diminished by use of antioxidant combinations. The reversion of the oral mucosa dysplastic changes was more evident in the patients using antioxidative vitamins that stopped smoking and ingestion of alcohol.

There are no studies regarding the efficacy of the use of L-AA alone for OL treatment.

B. α-Tocoferol (Vitamin E): α-Tocoferol (AT) is the commonest and most active form of vitamin E. Source: It is found in plant oil, margarine, and green leaves.

The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women. Its absorption rate is reduced when consumption exceeds 30mg/day. α-Tocoferol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation.

Erhardt et al. showed that supplementation with AT led to a significant rise in the concentration of this antioxidant in the plasma. In contrast, supplementation did not lead to a significant increase in the concentration of AT in cells of the oral mucous membrane.

C. Retinoic Acid (Vitamin A): The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Vitamin A exists in the human body as various inter convertible compounds, notably retinal (essential for vision) and retinol, which is the most potent analogue and the main form of storage and transportation. Source: 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.

The absorption of retinoids increases by up to 50% when ingested with food. Retinoids are transported in the blood by plasmatic proteins. Hepatic metabolization is achieved via the action of cytochrome P-450. Hyper vitaminosis occurs when consumption exceeds the liver’s capacity to store retinoids.

Topic retinoid were initially tested against diseases related to keratinization. 13-cRA was used for the first time against acne, in 1969. The so-called “retinoic dermatitis” is the main side effect of tretinoin, this leads to cutaneous irritation characterized by erythema, scaling, aridency, and/or pruritus. “Retinoic dermatitis” occurs frequently, and patients ought to be previously instructed with regard to its occurrence. Furthermore, patients should also be warned to avoid the sunlight and to wear sunscreen.

Systemic retinoids is not indicated in cases of (1) pregnancy or probability of pregnancy; (2) noncompliance with the use of contraceptives; (3) breast feeding; (4) hypersensitivity to parabeno (in isotretinoin capsules). It is, relatively, not indicated in cases of (1) leukopenia; (2) hypothyroidism.
(patients using bexarotene); (3) high levels of cholesterol and triglyceride; (4) hepatic malfunction; (5) renal malfunction. Absorption of systemic retinoids is boosted by up to 60% when they are taken together with the meals.

Supplementation with retinoids for OL treatment began in the 1960s. However, this treatment was not widely accepted due to its side effects. Side effects: Hypervitaminosis, toxicity, teratogenic effects, and alterations in various organic systems.

At the cellular-level, retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus by various proteins. Retinoids affect diverse processes, such as keratin production, the expression of growth factors and kinases, oncogenesis, apoptosis, production of the collagen matrix, immunologic and inflammatory response, cellular differentiation, morphogenesis and carcinogenesis.

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

Various studies have evaluated the therapeutic effectiveness of vitamin A derivatives in the treatment of OL, although not all studies have shown concordant results.

In one study, of the 45 patients registered, 7 (15.5%) had OL. 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.

A study conducted with retinoic supplementation (300,000 IU retinol acetate) for OL treatment demonstrated complete resolution in 52% of patients. Side effects observed included six patients with headaches, five patients reported muscle pain, and two patients reported dry mouth.

Kaugars et al. implemented retinoic supplementation in various dosages for OL treatment. Fifty percent of patients had complete or partial clinical resolution of OL, but with side effects such as dizziness and headache. Moreover, for most of the patients with clinical resolution of the lesion, OL recurred upon the discontinuance of medication. Some patients ceased treatment due to its side-effects.

On the other hand, during the assessment of 13-cRA topical use (0.1% isotretinoin gel) for 4 months, in 9 patients with OL, 20% showed complete clinical response to treatment and no patient reported adverse effects.

In another study, 13-cRA was used in 16 patients with OL for six months. Three patients were entered at a dosage of 3 mg/day, eight at 5 mg/day, and five at 10 mg/day. Eleven patients completed the study: 3 had complete clinical responses (2 at 10mg/day and 1 at 5 mg/day). Recurrence was observed in two of these three patients.

During another study, patients with OL were distributed into two groups: one receiving 200,000 IU vitamin A per week (n=21) and the other receiving placebo capsules (n=33) for six months. Complete remission was observed in 57% of patients that received vitamin A.

The administered doses of vitamin A did not produce any detectable adverse effects during the trial period. In the placebo group, 7 patients (21%) formed new OL; whereas no new OL developed in the vitamin A group over the 6 months.

In an additional study from these same authors, patients with OL were divided into three groups receiving: group 1, beta-carotene (180 mg/week); group 2, beta-carotene (180 mg/week) plus vitamin A (100,000 IU/week), and group 3 placebo, for 6 months. Remission of OL in group 1 (14.8%) and group 2 (27.5%) differed significantly from that seen in group 3 (3%). During the trial period, all patients continued to chew tobacco-containing betel quids.

Studies focusing on topical vitamin A and their derivatives in the management of patients with OL have been reviewed by Gorsky and Epstein. The use of topical tretinoin at 0.05% was evaluated in
26 patients with OL. Patients were followed for a mean of 23 months. Ten patients who had partial or no clinical response were submitted at biopsies pre- and post treatment, and the mean grade of histological features did not change. Twenty-seven percent of the patients had a complete clinical remission. Recurrence of OL was observed in approximately 40% of these patients after cessation of the applications. The use of topical vitamin A acid showed a limited effect in controlling OL.26

In an open trial, the clinical efficacy of topical calcipotriol (vitamin D3 analogue) was compared with tretinoin in the therapy of hyperkeratotic oral lesions (leukoplakia). Forty patients had histologically proven OL, 20 were treated with calcipotriol (50mg/g), and the other 20 with tretinoin cream (0.05%). The treatment was given for 5 weeks and follow up was at 4 months, with clinical assessments at 2, 4, and 5 weeks. Results showed complete resolution of OL in 16 patients in both calcipotriol and tretinoin groups. No documented topical or systemic adverse reactions and results were maintained at 4 months.27

D. 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, 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. 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.28

Eight patients with diffuse (non operable) oral lichen or OL were treated with 4-HPR applied topically twice daily. After one month of therapy, two patients had complete remission and the other six had a greater than 75% response. 4-HPR was well tolerated, and no local or distant side effects were observed.

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.29

Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of 12 patients.5

3. Anti-neoplastic agents:

A. Bleomycin: It is a cytotoxic antibiotic which was first used for the treatment of neoplasms of the penis and scrotum, but has also been employed for squamous cell carcinoma of the head and neck region, oesophagus, and skin.

The most commonly adverse effects are mucocutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin.20

Eight patients with OL were treated by the daily application of a 0.5% (w/v) solution of bleomycin sulphate in dimethyl sulphoxide (DMSO). After 12 to 15 applications, the white patch peeled off and the resultant raw surface was epithelialized over the following 14 days. Repeated biopsies showed a significant reduction of dysplasia and keratinisation. The use of topical 1% bleomycin in DMSO was evaluated for the treatment of dysplastic OL.20

Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients. It was well tolerated with minor mucosal reactions. Immediate post treatment biopsies showed that 75% of patients had resolution of dysplasia. Ninety-four percent of the patients attained at least partial clinical resolution. After a mean follow-up period of 3.4 years, 31.6% of patients had no clinically visible lesions. In 2 patients (11%), malignant transformation occurred.5

Topical bleomycin in treatment of OL was used in dosages of 0.5%/day for 12 to 15 days or 1%/day for 14 days.
Indications: Topical administration of bleomycin usually reduces lesion size and has little toxic side effects. It is beneficial to use bleomycin adjuvant with the surgical procedure for extensive leukoplakia to decrease the size of lesion before surgery. This helps to avoid grafting after removal of the lesion and prevent the dysplastic change of benign form of lesion. 2 weeks of daily topical application of bleomycin in dimethylsulphoxide (DMSO) painted over the lesion. The topical application of bleomycin is still in an experimental phase.5

B. 5-Fluorouracil: 5-fluorouracil (5-FU) has been widely used for chemotherapy of head and neck cancer, and is known to affect the cell cycle and induce apoptotic death of cancer cells. However, the molecular actions of 5-FU on the cell cycle regulatory mechanism have not been fully explained. 5-FU-induces changes in cell cycle regulation of oral cancer cells, which might be associated with an alteration of G1 cyclins expression.30

1. Photodynamic Therapy: Photodynamic therapy (PDT) is a noninvasive method for the treatment of premalignant lesions and head and neck cancers.31, 32 The principle of PDT is a non thermal photochemical reaction, which requires the simultaneous presence of a photo sensitising drug (photo sensitiser), oxygen, and visible light. After a period to allow the photo sensitiser 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 fibers to or into the tumor. Illumination of the tumor by light at the activating wavelength results in the destruction of cells by a non free radical oxidative process. These reactive oxygen species may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids.

Advantages: 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.32

Several photosensitisers have been developed during the past. Haematoporphyrin and haematoporphyrin derivatives were the first photosensitisers. Four photosensitisers have been approved so far: (1) Photofrin has been approved in many countries for the treatment of esophagus 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 2001.33

The ALA is a naturally occurring compound in the haem biosynthetic pathway, which is metabolized to a photosensitive product, protoporphyrin IX (PpIX). The major advantage of ALA when compared to synthetic photosensitisers is the rapid metabolism, which significantly reduces the period of cutaneous photosensitivity. For most indications in head and neck surgery, the photosensitiser is administered systemically by intravenous injection. 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.33

III) Surgical Treatment Modalities

In the event of no relief from non surgical modalities we need to go for surgical management. Surgical excision (scalpel), cryosurgery and CO₂ laser evaporation can be used for treatment of leukoplakia with good cure rates.

Conclusion

All individuals with leukoplakia, and those who were treated for it, should be educated to quit using tobacco use, and followed-up regularly. Since malignant transformation is high, tobacco usage over several years remains a major etiologic factor in particular, smoking tobacco although chewing and other forms of smokeless tobacco are proven causes of mucosal alterations as well. The role of public health programmes dealing with tobacco habits and tobacco deaddiction programmes cannot be overstressed.
Once detected, measures should be implemented for resolution of the lesion by using non surgical & surgical treatment modalities.

References:


