

A Review of the Nonsurgical Management of Oral Leukoplakia**Darshna Chowdhury, S.Y. Rajan, Padmavathi B.N., Gagandeep Kaur**

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ABSTRACT:

Leukoplakia is the most frequent oral potentially malignant disorder. Its diagnosis is established on clinical and histological basis. The main aim of oral leukoplakia management is to avoid malignant transformation. This is achieved by habit counselling for tobacco dependence and use of chemo preventive agents after diagnosis of leukoplakia or total surgical removal of the lesion. The aim of this review is to assess the nonsurgical treatment modality of oral leukoplakia.

Keywords: Leukoplakia, Non-surgical treatment, Lycopene.**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” (Axell et al 1983).¹ Leukoplakia’s etiopathogenesis encompasses two broad categories: leukoplakia of unknown etiology or idiopathic and leukoplakia associated with tobacco use.² There are two major clinical forms of leukoplakia: homogenous and non-homogeneous. The homogenous type has a flat, thin and smooth surface. The non-homogenous form can be speckled, verrucous or nodular. Leukoplakia can be a single lesion or it affects many locations thus being multifocal which is not considered a good sign. Proliferative verrucous leukoplakia is a long term progressive form which initially is homogenous, the slowly grows and spread. Lately it involves multiple mucosal areas with confluent, exophytic and proliferative features. This kind of leukoplakia is reluctant to any treatment, and has a high recurrence rate and progress to verrucous carcinoma or squamous cell carcinoma in the range 40-100%.³ Leukoplakia has an annual malignant transformation rate of 0.1% to 17%.

Some factors may contribute to increase the chance of the leukoplakia to become malignant

these include the following: female patients, a long-time lesion which is resistant to the treatments, lesions in the floor of mouth, ventrolateral surface of tongue and soft palate have a higher chances of malignant transformation. Nonsmokers have more chance of malignant transformation as compared to smokers, leukoplakia lesions have a mixed color of white and red alterations and an exophytic, papillary, or verrucous aspect often eventually transformation to squamous cell carcinoma. Leukoplakia with moderate and severe dysplastic lesions had a significantly higher risk of developing a squamous cell carcinoma than leukoplakia without epithelial dysplasia or with mild epithelial dysplasia.⁴

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 lesion 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 those 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 leukoplakia, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. However, 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.^{3,4} Nonsurgical treatment modality offers minimal adverse effects to patients, especially for patients with widespread 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 leukoplakia include easy application that does not require treatment at a medical center and relative low cost.⁷

Nonsurgical Treatment modalities

1. Behavior Modification:

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. Up to 60% of leukoplakia regress or totally disappear if tobacco use is stopped. Leukoplakia induced by smokeless tobacco may resolve if the habit is stopped. Some candidal leukoplakia respond, at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress.⁵ Counselling along with medication used for tobacco cessation has shown high abstinence rate, that is why pharmacotherapy should be initiated at earliest in cases of tobacco cessation.(TABLE 1). Pharmacotherapy has to be initiated at least a week before the quit date for better results.⁶

2. Carotenoids

A. Beta-Carotene

Beta-carotene is a vitamin A precursor. Beta-carotene is a carotenoid commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. Beta-carotene function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of freeradicals.⁷ In few studies it has been reported that with dosage regimes of 20 to 90mg/ day of beta-carotene for 3 to 12 months has shown 4% to 54 of clinical resolution of oral leukoplakia.⁷ Results from Sankaranarayanan et al. demonstrated that 15 out of 46 patient who were treated with 360 mg beta-carotene per week for 1 year. After 1 year of treatment 8 out of 15 patients has shown complete response and 2 out of 15 developed malignant neoplasia adjacent to oral leukoplakia lesion.⁸

B. Lycopene

Lycopene is a carotenoid without provitamin A action. It is a fat-soluble red pigment found in some fruit and vegetables. 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.¹⁰ Singh et al conducted a study on 58 patients to assess the efficacy of lycopene for the treatment leukoplakia. Three groups were made, and received 8 mg/day, 4 mg/day, and placebo for 3 months. The patients receiving 8 mg/day and 4 mg/day lycopene has shown 55% and 25% complete clinical response.⁹

3. Vitamins:

A. L-Ascorbic Acid

L-ascorbic acid (L-AA), the so-called vitamin C. Sources are Citrus fruits such as kiwi, strawberries, papaya, and mango. In a study subjects with low plasma L-AA levels formed the study group and individuals with normal L-AA levels formed the control group and

they were compared. Oral mucosal lesions in all subjects were defined clinically as petechias, leukoplakia, and lichenoid lesions and found that there was a statistically significant difference between the groups only for leukoplakia, where the prevalence of leukoplakia was higher when smoking was combined with LAA deficiency.¹¹ In another study, 24 leukoplakia 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.¹²

B. α -Tocoferol (Vitamin E)

It is the commonest and most active form of vitamin E. α -Tocoferol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation. Erhardt et al. showed that supplementation with α -Tocoferol led to a significant rise in the concentration of this antioxidant in the plasma.¹³

Benner et al evaluated the toxicity and efficacy of α -Tocoferol in 43 patients with leukoplakia 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 α -Tocoferol levels. He found that 10 patients has shown complete clinical remission, 10 patients has shown and 9 has shown complete reversal of dysplasia to normal epithelium. Mean serum α -Tocoferol levels were 16.1 μ g/mL at baseline and increased to 34.29 μ g/mL after 24 weeks of treatment.⁷

Seventy-nine patients with leukoplakia were enrolled in an antioxidant supplementation program that consisted of 30 mg of beta-carotene, 1000 mg of L-AA, and 800 IU of AT per day, which were taken for 9 months. No side effects were noticed during the course of the study. He observed 90% clinical

improvement in those patients who had reduced risk factors and 48.8% of improvement in those who did not and few patients developed squamous cell carcinoma within the pre existing leukoplakia during or shortly after completion of the study.⁷

C. Retinoic Acid (Vitamin A)

13-cRA is the retinoid recommended for leukoplakia treatment. However, the high recurrence rates after short periods of discontinuance, together with its side effects like hypervitaminosis, toxicity, teratogenic effects, and alterations in various organic systems, are limiting factors.^{14,15} In the systemic use with dosage of 300.000 IU of retinoic acid, a clinical resolution of the 50% has been demonstrated.⁷ In a recent study the results obtained on using topical retinoid for the treatment of proliferative verrucous leukoplakia, involving variable concentration of tretinoin or isotretinoin in gel form (0.05% to 0.1%), are generally similar to those obtained with systemic retinoid.¹⁶

A study conducted with retinoic acid supplementation (300.000 IU retinol acetate) for leukoplakia treatment demonstrated complete resolution in 52% of patients.⁸

In one study, out of the 45 patients, 7 had leukoplakia. They were treated with 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. 71% of leukoplakia patients had shown complete clinical responses.¹⁷

Kaugars et al. conducted a study in which retinoic acid supplementation were given for the treatment of leukoplakia. Fifty percent of patients had complete or partial clinical resolution of leukoplakia, but with side effects such as dizziness and headache. In most of the patients with clinical resolution of the lesion, leukoplakia recurred after discontinuance of treatment. During the assessment of 13-cRA topical use (0.1% isotretinoin gel) for 4 months, in 9 patients with leukoplakia, 20% showed complete clinical response to treatment with no adverse effects.¹⁵

D. Fenretinide

Fenretinide (4-HPR) is a vitamin A analogue. It has proved that it is 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.¹⁸ In a study 4-HPR applied topically twice daily in 8 patients who were diagnosed with non operable oral lichen or leukoplakia. After one month of therapy they noticed that 2 patients had shown complete remission and the other 6 had a greater than 75% response and no local or distant side effects were observed. In an phase II trial of 4-HPR (200 mg/day) was carried out for 3 months in leukoplakia patients who had not responded or who had responded and then relapsed to the previous treatment with natural retinoids. Of 35 patients with retinoid-resistant leukoplakia, 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.¹⁹ Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of leukoplakia of 12 patients.⁷

4. Anti-neoplastic agents:

A. Bleomycin

Topical bleomycin in treatment of leukoplakia was used in dosages of 0.5%/day for 12 to 15 days or 1%/day for 14 days.⁵ In a study 80 patients with leukoplakia were treated by the daily application of a 0.5% (w/v) solution of bleomycin sulphate in dimethyl sulphoxide and observed that after 12 to 15 applications, the white patch peeled off and the raw surface was epithelialized after 14 days. Repeated biopsies showed a significant reduction of dysplasia and keratinisation. The use of topical 1% bleomycin in sulphate in dimethyl sulphoxide was evaluated for the treatment of dysplastic leukoplakia.¹⁴ Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients and after immediate post treatment biopsies observed that 75% of patients had resolution

of dysplasia and 94% of the patients attained at least partial clinical resolution. After the follow-up period of 3.4 years, 31.6% of patients had no clinically visible lesions and in 2 patients, malignant transformation occurred.

5. Photodynamic Therapy

Photodynamic therapy (PDT) is a non invasive method for the treatment of premalignant lesions and head and neck cancers.^{20,21} The principle of PDT is a non thermal photochemical reaction, which requires the simultaneous presence of a photo sensitising drug, oxygen, and visible light. These reactive oxygen species may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids.

Advantages of PDT are low systemic toxicity, damage heals mainly by regeneration and structures are maintained with good functional and cosmetic outcome.²¹ Four photosensitisers have been approved so far: Photofrin, 5-Aminolaevulinic acid (ALA), Verteporfin and Foscan.²² A study was conducted on 44 patients having leukoplakia, photodynamic therapy was performed for 10 illumination session and significant reduction was found in the size of the lesion.²³ In another study 5 patients with leukoplakia were treated with 10% of 5-Aminolaevulinic acid mediated photodynamic therapy and concluded that there is a satisfactory reduction in the size of lesion without any side-effects.²⁴ Chen et al treated patients with leukoplakia using 20% Aminolaevulinic acid mediated photodynamic therapy and found satisfactory reduction. From the studies using Aminolaevulinic acid mediated photodynamic therapy in topical concentrations from 10 to 20%, it may be observed a clinical resolution of leukoplakia of the 25% to 80%.²⁵

DISCUSSION AND CONCLUSION

In order to conduct treatment for leukoplakia, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. However, 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. Leukoplakia surgical treatment maybe performed either through conventional surgery, electro cauterization, laser ablation, or cryosurgery. However, it has been shown that surgical intervention does not appear to

prevent leukoplakia from developing recurrence. Malignant transformation of these lesions is independent of drug or laser therapy.²⁸

Nonsurgical intervention is chosen in cases where the lesions involve a large area of the oral mucosa, when patients present with high-risk medical problems for surgery, or when patients refuse surgical intervention and after follow-up without surgery.²⁸

Pharmacotherapy	Side effects	Dosage and Duration
NICOTINE REPLACEMENT THERAPY		
1. Nicotine Patch	Local skin reaction Insomnia	<ul style="list-style-type: none"> • 21 mg/24 hours for 4 weeks • 14 mg/24 hours for 2 weeks • 7 mg/24 hours for 2 weeks
2. Nicotine Gum	Mouth soreness Dyspepsia	<ul style="list-style-type: none"> • 1 -24 cigs/day-2mg gum [up to 24 pcs/day] • 25+cigs/day-4mg gum [Up to 24 pcs/day] Up to 12weeks
3. Nicotine Lozenge	Nausea Insomnia	<ul style="list-style-type: none"> • If patient smokes more than 30 min. after waking -2 mg lozenge • If smokes less than 30 min. after waking • 4 mg lozenge Not more than 20 lozenges per day Up to 12 weeks
4. Nicotine Inhaler	Local irritation of mouth and throat	6-16 cartridges/day Each cartridge is 4mg in 80 inhalations Up to 12 weeks.
5. Nicotine Nasal Spray	Nasal irritation	-0.5 mg in each nostril 1 to 2 doses per hour . 8-40 doses/day for a period of 3 to 6 months
MEDICATION THAT MIMIC TOBACCO EFFECTS		
1. Bupropion SR	Insomnia Dry mouth	150 mg every morning for 3days,then 150mg twice daily 7-12 weeks and up to 6 months.
2. Varenicline	Mild to moderate nausea	0.5 mg once a day for 1-3 days. 0.5 mg twice a day for 4-7 days. 1 mg twice a day from day 8 to end of treatment which is for a duration of 12 weeks.

Table 1: Drugs Used in Tobacco Dependence

In the lesions in which dysplasia is present but excision is not possible those lesions can be treated by lycopene, other antioxidants and topical bleomycin and those lesions in which dysplasia is absent those can be treated by vitamin A analog.²⁹

Owing to progressive nature of Proliferative verrucous leukoplakia, many types of therapies

has been used like CO₂ laser, topical bleomycin solution, oral retinoids, beta carotene and systemic chemotherapy have failed at achieving permanent cure. Methisoprinol have shown some clinical efficacy in HPV- induced lesions. Laser ablation reportedly has been successful in a very small group of patients followed for 6-

178 months. Surgical shave followed by cryosurgery and photodynamic therapy have also been suggested. Topical photodynamic therapy also may prove useful; it causes relatively low morbidity and no scarring and multiple mucosal sites can be treated simultaneously.^{30,31}

Non surgical treatment includes counselling delivered by physicians and other professionals significantly increases quit rates of tobacco over self initiated strategies. Counselling with medication has shown significantly high continuous abstinence rates.⁶ The use of beta-carotene has been recommended in order to prevent leukoplakia and possibly oral cancer.^{26,27} In the revised studies, the percentage of patients with clinical resolution ranged from 4% to 54%, with dosages regimes from 20 to 90 mg/day of beta-carotene in time periods from 3 to 12 months.^{7,8}

Lycopene appears to be a very promising antioxidant at the dosage of 8mg /day as a treatment modality in oral leukoplakia. In few studies results indicated that lycopene can protect cells against cell damage and play a protective role against progression of dysplasia.⁹

L-ascorbic acid is used in combination with beta carotene and vitamin E because they act synergistically to enhance individual action to achieve antioxidant action. In one study, leukoplakia patients were treated with an association of beta-carotene, vitamin E, and L-ascorbic acid, and an increase was observed in the reversion of oral mucosa dysplasia.¹²

Retinoids are promising chemopreventive agents.13-cRA is the retinoid recommended for leukoplakia treatment. The use of 13-cRA has been shown to be effective in resolving leukoplakia. However, the high recurrence rates after short periods of discontinuance, together with its side effects, are limiting factors.¹⁵

α -Tocoferol used in combination with beta carotene and vitamin E because they act synergistically to enhance individual action to achieve antioxidant action. α -Tocoferol had

shown few complete and partial clinical remission of lesion.⁷

Fenretinide has been used in few studies both topically and systemically for the treatment of leukoplakia and both way of administration has shown partial clinical remission and toxicity was minimal.⁷

Bleomycin is a cytotoxic antibiotic. 0.5% and 1% (w/v) solution of bleomycin sulphate in dimethyl sulphoxide (DMSO) is used for treatment of leukoplakia and in few studies repeated biopsies showed a significant reduction of dysplasia and keratinisation.⁷

Photodynamic therapy with 5-Aminolaevulinic acid in topical concentrations from 10 to 20%, has shown clinical resolution of leukoplakia up to 25% to 80%.⁷

From the above literature it can be concluded that few treatments may be effective for the healing of the leukoplakia but not able to prevent the relapses and malignant transformation. For this reason, all individuals with leukoplakia, and those who were treated for it, should be educated to quit using tobacco use, and followed-up regularly regardless of their response to topical or systemic treatment, including clinical resolution to prevent its malignant transformation.

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