MANAGEMENT OF ORAL LEUKOPLAKIA - ANALYSIS OF THE LITERATURE

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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.

The aim of this article is to present a review of the management of oral leukoplakia according to the literature until now.

Management of oral leukoplakia should begin with elimination of risk factors (if any) such as tobacco abuse, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc.

Conservative treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (beta-carotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcuma etc.

Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation).

The main purpose of oral leukoplakia management is to avoid malignant transformation of the lesion or if this happened to detect this in early stages.

Keywords: Leukoplakia, management, surgical, non-surgical treatment,

INTRODUCTION

Oral leukoplakia (OL) is the most frequent precancerous lesion of the oral cavity. [1, 2] Oral leukoplakia is defined by WHO (1997) as "a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion". [2, 3, 4]

In 2012 van der Waal [5] proposed a new definition which seems more oportune as it includes the histological confirmation: "A predominantly white lesion or plaque of questionable behavior having excluded, clinically and histopathologically, any other definable white disease or disorder". This one hasn't been assessed yet by WHO but it has good chances for acceptance by the physicians.

Purpose

The aim of this article is to present a review of the management of oral leukoplakia according to the contemporary standards.

MATERIAL AND METHODS

An electronic search (MEDLINE, EMBASE, and controlled clinical trials (CCT) were reviewed. 18 articles were chosen and analyzed about management of different types of oral leukoplakia.

RESULTS AND DISCUSSION
Epidemiology

The prevalence of oral leukoplakia, worldwide, is approximately 1%-2% for all ages together. There are geographical differences with regard to gender distribution. Leukoplakias are usually diagnosed after the fourth decade of life and are six times more common among smokers than among non-smokers. Alcohol may be an independent or synergistic risk factor. There may be a potentially important and causal association between human papillomavirus and oral potentially malignant disorders.

Erythroplakia is much less common than leukoplakia. No reliable prevalence figures are available; estimated figures vary from 0.02% to 0.83%.The etiology is unknown, but tobacco and alcohol are probably predisposing factors.

Etiology

Etiology of OL is not clearly established yet. [4] It is considered multifactorial origin of the lesion. [5] Smoking, alcohol abuse, lasting mechanical injuries, Candida albicans infection and differences of local trauma or galvanic potentials are reported as the most important causative factors. Oral leukoplakia can accompany systemic disorders like hormonal disturbances, gastroaesofagal reflux, diminished saliva secretion or iron deficiency anemia. It is also stated that EBV, HPV (16 and 18 types), HSV and HIV viruses significantly influence OL development and carcinogenic transformation of this lesion. [4]

Classification/clinical aspects

Considering the **macroscopic appearance**, oral leukoplakia is broadly classified into *homogeneous* and *non-homogeneous* subtypes.[2, 3]

The distinction between this two types is purely clinical, based on surface colour and morphological (thickness) characteristics, and do have some bearing on the outcome or prognosis. [6]

Homogeneous plaques are predominantly white, of uniform flat, thin appearance with shallow cracks of sur-

face keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout. [2, 3] Despite the fact that the risk of malignant transformation is relatively low - about 5% [6], these lesions seem to warrant careful follow-up as well. [7]

Non-homogeneous plaques varieties include [6]:
• speckled: mixed, white and red (erythroleukoplakia), but retaining predominantly white character;
• nodular: small polypoid outgrowths, rounded red or white excrescences;
• verrucous: wrinkled or corrugated surface appearance.
• proliferative verrucous leukoplakia (PVL). Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia according to some authors[3,6]. It involves multiple mucosal areas with confuent, exophytic and proliferative features. [2] The PVL is characterised by an aggressive evolution, resistance to treatment, and high rate of malignant transformation. [3, 5]

Non-homogeneous lesions carry a higher risk of malignant transformation. [6]

Additional clinical descriptions that may assist the characterization of oral leukoplakia are [6]:
· Etiological description: clearly associated with tobacco or areca nut use; idiopathic.
· Site description giving anatomical sub-site in the mouth or oropharynx.
· Size or extent of the lesion(s).

Leukoplakia is a clinical term and the lesion has no specific **histology.** [6] Pathohystological examination of leukoplakia can show hyperkeratosis, atrophy, acanthosis and may or may not demonstrate different degrees of epithelial dysplasia. [2, 6] Dysplasia reflects histological changes which are followed by the loss of uniformity of the architecture of the epithelial cells.[5]

According to these findings, oral leukoplakia can be distinguished as **dysplastic and non dysplastic** lesions. Based on histological examination the presence of dysplasia has been associated with a risk of malignant transformation to oral cancer. [3]

At the last world seminar of Oral Medicine about potentially malignant lesions, London 2010, it has been recommended a binary classification of histological changes. [5] Lesions are graded as low risk (mild and moderate dysplasia) and high risk (severe dysplasia and carcinoma in situ) depending on the architecture and cytological changes. [3] This aims to reduce subjectivity in grading dysplasia, thus increasing the possibility of conformity between histological interpretations of different pathologists. [5]

Epithelial dysplasia has been regarded as one of the most important indicators of future malignant potential. [3] Dysplastic oral leukoplakia has a 5 times higher risk of malignant transformation than non-dysplastic. [2, 3] A study showed that for a period of 5 years follow-up dysplastic lesions had a incidence of malignant transformation of 41%

and non-dysplastic lesions just 9.5%. [2]

It must be noted that oral epithelial dysplasia has no specific clinical appearance.[6] It can be present in any apparently benign clinical white lesion. [2]

Despite advances in molecular biology, nowadays there are no reliable markers to predict the malignant transformation of oral leukoplakia. It has been reported that a few markers such as Ki-67 (Mib-1) and bromodeoxyuridine, and the combined biomarker score of chromosomal polysomy, p53, and loss of heterozygosity might be strong predictors for malignant transformation, but this is not generally adopted in clinical practice.[2, 3]

The risk factors for malignant transformation include age, site, size, appearance, presence of dysplasia, and abnormal DNA content, but there is no single predictive factor or any reliable biomarker predictive of malignant transformation. [3]

Main factors associated with increased risk of malignant transformation are patients who do not smoke and are over 60 years of age; lesions that are non-homogeneous or are wide spread; lesions located in high-risk areas and those larger than $200mm^2$; and histopathologically confirmed epithelial dysplasia. [3]

High-risk areas for malignant transformation have been identified as floor of the mouth, lateral borders of the tongue, soft palate and retromolar areas. [8]

According to some authors high malignant incidences for patients with high-grade dysplasia occurred during the first 2–3 years of follow-up. [8]

The patients with histologically confirmed leukoplakia are reported to have no malignant transformation in 86.6% after 3 years of follow-up and 82.0% after 5 years. [2]

Although clinical appearance such as non-homogeneous oral leukoplakia and anatomical site (notably the floor of the mouth and the ventral tongue) can help to identify lesions with a high risk of malignant transformation, there are no reliable ways to predict the behavior of individual lesions or to guide clinical management without biopsy examination. [3]

Patients with multiple oral precancerous lesions and extensive areas of mucosa that may show signs of dysplastic change are particularly difficult to manage. Modern concepts of carcinogenesis have emphasised the existence of molecularly altered preneoplastic fields (field of cancerization) from which multiple lesions can develop. Widespread lesions have been shown to have higher rates of malignant transformation than those that are more localized. [3]

DIAGNOSIS

Histopathology examination is at present still the gold standard for diagnostic purposes. DNA ploidy measurements may be helpful in identifying lesions that carry a high risk of malignant transformation.

The biopsy should be taken at the most clinically suspicious area, if any, such as redness, an area of surface thickening or a symptomatic area. In patients with multifocal or widespread leukoplakia multiple biopsies ('field mapping') should be considered. Particularly in the case of a

non-homogeneous leukoplakia an incisional biopsy may not be representative. In small leukoplakias, e.g. < 2 - 3 cm, an excisional biopsy may be considered. The value of oral brush cytology is a subject of controversy, as is the use of toluidine blue. [7, 8]

Malignancies may develop at the site of treated or untreated leukoplakia, but may also occur elsewhere in the oral cavity or upper aerodigestive tract. The commonly recognized factors that statistically carry an increased risk of malignant transformation into a squamous cell carcinoma are listed below. Of these risk factors, the presence of epithelial dysplasia – often correlating with a clinically non-homogeneous, erythroleukoplakic subtype – is in general regarded the most important indicator of malignant potential. Nevertheless, it should be recognized that some dysplastic lesions may remain unchanged or may even show complete regression.

Furthermore, carcinomatous transformation may also take place in non-dysplastic leukoplakia.

In several studies from the Western world, the borders of the tongue and the floor of the mouth have been mentioned as high-risk sites, while in a study from Denmark also size was shown to be of importance, particularly when exceeding 200 mm^2.

In spite of tremendous progress in the field of molecular biology, there is as yet no single marker or set of markers that reliably enables to predict malignant transformation of leukoplakia in an individual patient with leukoplakia, perhaps with the exception of DNA ploidy measurements. The use of non-invasive genetic tests, using exfoliated or brushed cells of lesional tissue or molecular markers from saliva may prove to be a step forward in the search for relevant prognostic markers . Most erythroplakias will probably undergo malignant transformation. There are not enough documented series that would allow to calculate a reliable annual malignant transformation rate.

Reported risk factors of statistical significance for malignant transformation of leukoplakia, listed in an at random order (not reliable for use in the individual patient)
· Female gender
· Long duration of leukoplakia
· Leukoplakia in non-smokers(idiopathic leukoplakia)
· Location on the tongue and/or floor of the mouth
· Size >200 mm^2
· Non-homogeneous type
· Presence o *C. albicans*
· Presence of epithelial dysplasia
· DNA aneuploidy
· History of previous head-and-neck carcinoma

Even though numerous manuscripts have dealt with management of oral leukoplakia, still there is lack of a proper protocol and no universal consensus on its management. [9] The standard treatments for OL range from careful consideration to complete excision in histological clear margins. [4]

Even despite treatment the disease can recur, undergo malignant transformation, or new lesions can develop in patients treated previously. [3]

Various **non-surgical and surgical treatments** have been reported, but currently there is no consensus on which is best. [3] The main aim of oral leukoplakia management is to avoid malignant transformation. [2]

Proper clinical examination should be done on the day of reporting of the lesion; type, size and location of lesion should be carefully recorded. [9]

A consideration of their risk potential i.e. low risk leukoplakia and high risk leukoplakia should be done. [9, 10]

Low risk leukoplakia: Leukoplakia lesions 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 200 mm
c. Homogenous clinical form

High risk leukoplakia: A leukoplakia is considered to be at a high risk if it shows dysplasia associated with following features:
a. Site in high risk area
b. Size greater than 200mm
c. Non homogenous clinical form [9, 10]

Differential diagnosis

White lesions of oral mucosa often present problems of differential diagnosis, which are of primary importance when assessing precancerous changes in the mouth. The precancerous character of oral leukoplakia is well established, and the "high-risk" type: erosive-dysplastic leukoplakia of greater malignant potential has been thoroughly investigated. Because of their possible association with oral carcinoma, some clinical types of oral lichen planus, namely, the atrophic-erosive forms indicate caution in their treatment and supervision. Epithelial dysplasia is often associated with candidiasis and discoid lupus erythematosus, but neither this, nor such other white lesions as white sponge naevus or morsicatio buccarum, are considered to be preneoplastic. All these white lesions may be clearly identified, differentiated, and circumscribed as clinicopathological disease-entities, by clinical, histopathological and ultrastructural methods, thus facilitating early diagnosis, treatment and prevention of possible malignancy.
• Leukoedema
• Lichen planus
• Chemical burn
• Morsicatio buccarum (habitual cheek biting)
• Candidosis
• Psoriasis
• Lupus erythematosus
• White sponge nevus

Management

Clinical examination is repeated after 2-3 weeks to assess the regression in size of lesion in low risk as well as high risk leukoplakia. After 2-3 weeks of habit cessation, if there is regression in size of leukoplakia than follow up is done initially every three months followed by every 6-12 months. [9]

Low risk lesion which is not regressing in size even after habit cessation or in cases of high risk lesion, biopsy is mandatory [9] in order to assess the degree of epithelial dysplasia. [4]

In cases which show no signs of dysplasia, then conservative treatment is advised. In cases of mild, moderate or severe dysplasia, both conservative and surgical treatment is advised. [9]

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, 10]

In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. [4]

Non-surgical treatment can be considered as a good choice in homogenic OL without dysplasia or as an initial treatment in other cases of OL. [1]

Non-surgical treatments cause minimal adverse effects, particularly in patients with widespread oral leukoplakia that involves a large area of the oral mucosa, or in those with medical problems who have high surgical risks, or when patients refuse surgical intervention. [3, 4, 10]

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. [10]

Treatment options

Any treatment of oral leukoplakia should begin with **elimination of risk factors** such as tobacco abuse, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc.

The ceasing of tobacco use is a prior action in case of tobacco associated leukoplakia. [2]

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. [10]

Counseling delivered by physicians and other professionals significantly increases tobacco quit rates. Even a brief (3-minute) period of counseling to urge smoker to quit results in smoking cessation rates of 5-10%. [9]

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. [10]

Conservative treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (beta-carotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcuma etc. [3, 9]

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy [9], thus reducing the morbidity and mortality associated with it. [11]

The use of photodynamic therapy has been also reported. [3]

Careful and routine follow-up observations of leukoplakia are appropriate in conjunction with elimination of any risk-associated behavior or habits. [10] In case of no improvement, treatment should become more invasive. [1]

Surgical treatment still remains one of the most common treatment methods in OL and should be the method of choice in OL with histologically diagnosed epithelial dysplasia. [1]

Surgical treatment includes conventional surgery, electrocoagulation, cryosurgery, and laser surgery (excision or evaporation). [3]

Surgical treatment for OL may prevent the development of oral squamous cell carcinoma, provided by assuring that the resection margins are adequately thick and free of epithelial abnormalities. However, it has been shown that surgical intervention does not appear to prevent OL from developing recurrence. Malignant transformation of these lesions is independent of drug or laser therapy. [4]

Non-surgical treatment of oral leukoplakia
1. Carotenoids
Carotenoids belong to a group of highly hydrophobic molecules with little or no solubility in water. [4, 10]

1.1. Beta-Carotene
Beta-carotene is a vitamin A precursor.[2, 4] This carotenoid is commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. [10]

The use of beta-carotene has been recommended for the prevention of potential malignant lesions, such as OL and cancer, possibly oral cancer. The potential benefits and protective effects against cancer are possibly related to its antioxidant action. [4]

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]

It has been shown that beta-carotene has a better therapeutic clinical response in preventing oral leukoplakia lesions in smokers than in nonsmokers.

A known side effect of excessive beta-carotene consumption is a change in skin color, which becomes very yellowish, called carotenoderma, which disappears in a few weeks after the reduction of consumption. [4]

Some studies report that clinical resolution of oral leukoplakia ranges from 4% to 54%, with dosages regimes from 20 to 90mg/day of beta-carotene in time periods from 3 to 12 months. [2, 4]

1.2. Lycopene
Lycopene is a fat-soluble red pigment found in some fruit and vegetables. [2] The greatest known source of

lycopene is tomatoes. [10]

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 cardio-vascular diseases. [2]

Lycopene appears to be a very promising antioxidant as a treatment modality in oral leukoplakia and can protect cells against damage.[4, 10]

In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to play a protective role against progression of dysplasia by inhibiting tumor cell proliferation. Lycopene brings about histological changes of a significant degree in patients with oral leukoplakia. [4, 10]

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. [10] Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb anti oncogenes and stop cell division at the Go-G 1 cell cycle phase. [9]

Some authors tried to estimate the relation between nutrient intake and prevalence of oral leukoplakia. They observed that tomato consumption, the main source of lycopene, has the most protective effect on oral leukoplakia among all dietary factors. [10] Lycopene is better absorbed in oil resin capsules and in tomato juice than in the form of raw tomatoes. [10]

A study evaluated lycopene in oral leukoplakia for a three months period, with dosages regimes from 4mg/day and 8mg/day and patients had clinical resolution 25 and 55%, respectively. [2]

It has been reported that a daily dose of 8 mg of lycopene was more effective than 4mg a day. [4]

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. [10]

2. Vitamins
2.1. Retinoids (Vitamin A/ Retinol)

The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. [2, 10]

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. [9]

Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins.[4, 10]

Vitamin A is required in the normal pathway of epithelial cell differentiation and production of keratin. [9] An association between vitamin A deficiency and the enhanced susceptibility to carcinogenesis was reported with an increased risk for developing different epithelial carcinomas. [9]

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.[4, 10]

Supplementation with retinoids for oral leukoplakia treatment begin in the 1960s, however, this treatment was not widely accepted due to its side effects-hypervitaminosis, teratogenic effects, toxicity, and alterations in various organic systems. [2, 4]

Topic retinoid were initially tested against diseases related to keratinization. [10]

Studies focusing on topical vitamin A and their derivates in the management of patients with OL have been reviewed by Gorsky and Epstein. [10] They used 0.05% tretinoin gel that was applied topically 4 times per day for the management of non-malignant oral white lesions in 26 patients (17 men and 9 women) with a mean age of 62 years. The vitamin A acid gel was applied locally for a mean of 3.5 years in patients who experienced clinical improvement. Although a complete clinical remission was reported in 27% of patients, a partial response was noted in 54% of patients, and clinical recurrence was experienced in about 50% of patients after the topical treatment was discontinued. Side effects of only a localized soreness were reported by only 19% of patients. [9]

The topical use of 13-cis retinoic acid has been shown to be effective in resolving oral leukoplakia. But they are limited because recurrences appear after short periods of cessation of the treatment. In the systemic use with dosage of 300.000 IU of retinoic acid, a clinical resolution of the 50% has been demonstrated. [2, 10]

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.[2]

2.2. 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. [11]

It is found in plant oil, margarine, and green leaves. [10]

Benner et al., in his trial in 1993 showed 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. [11]

On the other hand, Miller et al., performed a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized controlled trials. It was found that high doses of vitamin E supplementation (> 400 IU/d) may increase all-cause mortality and should be avoided. [11]

The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women. [10]

2.3. 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.[10] Vitamin C can be found in citrus fruits such as kiwi, strawberries, papaya, mango etc.

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. [10]

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. [10]

There are no studies regarding the efficacy of the use of L-AA alone for OL treatment. [10]

Some studies conducted a randomized controlled trial on treatment of oral leukoplakia with low dose of beta carotene and vitamin C supplements. Vitamin C in the study was neither effective for clinical remission, nor for protection against the development of cancer. [10, 11]

2.4. Fenretinide

The compound N- (4-hydroxyphenyl) retinamide, also known as fenretinide (4-HPR) was synthesized in the United States in 1960 and is used for treating OL. [4]

It has proven to be less toxic than many other vitamin A analogues. 4-HPR is well tolerated, and no local or distant side effects are observed. [10]

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. [10]

This compound is used for the chemo-preventive treatment of various diseases, and has been studied and tested in clinical trials for the treatment of OL. [4]

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. 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. Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of 12 patients.[10]

3. Anti-neoplastic agents:
3.1. Bleomycin

Bleomycin is a cytotoxic antibiotic which was first used for the treatment of neoplasms. It can be used as an alternative for treatment of oral leukoplakia. [2, 10] It is not very often used in practice for its adverse effects [2]

The most commonly adverse effects are muco-cutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin. [2, 10]

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. [10]

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. [10]

In a study, eight patients with OL were treated by the daily application of a 0.5% solution of bleomycin sulphate in dimethyl sulphoxide (DMSO). After 12 to 15 applications, the white patch peeled off and the resultant raw suface 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.

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. [10]

4. Polyphenols as chemo-preventive agents
4.1. Curcumin

Curcumin has been used for thousands of years in traditional Indian medicine. [12]

Curcumin 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 micronucleation. [13]

Small doses of curcumin are taken daily as a spice by the population in many Asian countries. In one epidemiologic survey, in terms of its dietary use in Nepal, curcumin consumption was found to be approx. 50 mg/day. In India, where the average intake of curcumin can be as high as 100 mg per day, no toxicities or adverse effects have been reported or studied at the population level. However the doses administered in clinical trials are expected to be rather higher than those normally consumed

in the diet. [14]

In spite of reported minor adverse effects, large doses of up to 12,000 mg per day of curcumin were found to be well tolerated in humans. Therefore, based on the safety and toxicity profile, in several clinical trials the targeted doses for curcumin can be recommended in between 4,000–8,000 mg to obtain the maximum therapeutic effects. [14]

In 2010, some clinicians conducted a study on patients aged 17-50 years, divided into three groups with 25 patients in each. The first group consisted of patients suffering from leukoplakia, while patients suffering from oral submucous fibrosis or lichen planus, and those in full health constituted the second and the third groups, respectively. Evaluation of markers of oxidative stress in saliva, serum in salivary glands (malondialdehyde (MDA), 8-hydroxy-22 -deoxyguanosine (8-OHd), and the level of vitamin C and E was made before administering curcumin to the patients, a week later, and after recovery.

It was noted that the markers in saliva, serum and vitamin level increased, whereas MDA and 8-OHd levels decreased simultaneously in patients suffering from leukoplakia, oral submucous fibrosis and lichen planus. Considering the results of the Rai et al. study, it can be assumed that curcumin demonstrates anticancer properties by increasing the levels of vitamins C and E, suppressing the peroxidation of lipids, and preventing DNA damage. [12]

Some authors observed the reduced size of the lesions in 10 of the 62 patients receiving topical turmeric/curcumin in oral cancers and leukoplakia, however the report is lacking the control group and standard method of curcumin preparation. [14]

A phase I clinical study performed in Taiwan investigated the potential anti-carcinogenesis activity of curcumin in patients with preinvasive malignant or high-risk premalignant conditions.25 patients with recently resected cancer of the bladder, Bowen disease of the skin, uterine cervical intraepithelial neoplasia, intestinal metaplasia of the stomach, or oral leukoplakia, were administered curcumin in doses of 1,000 to 8,000 mg (500 mg of synthetic curcumin per capsule, 99% purity) daily for three months. Histologic improvement of the premalignant lesions was noted in two of seven patients with oral leukoplakia. On the contrary, one of seven patients with oral leukoplakia developed malignancy despite the treatment. [14]

It seems that curcumin is a pluripotent pharmacological agent [13] and may be the new hope for reducing incidence of cancer and precancer. [12]

A trial study in USA (National Cancer Institute) investigate if metformin hydrochloride works well in preventing oral cancer in patients with an oral premalignant lesion (oral leukoplakia or erythroplakia). These lesions can be associated with a higher risk of cancer. Another study also in USA evaluate prevention of oral cancer in patients with an oral premalignant lesion by using Metformin Hydrochloride in combination with curcuminin. They thing that Metformin hydrochloride in combination with curcumin may help prevent oral cancer from forming in patients with an oral premalignant lesion.

4.2. Green Tea Polyphenols

Epigallocatechin gallate (EGCG), a major polyphenol found in green tea possesses antioxidant and chemo-preventive properties. Epigallocatechin gallate (EGCG) shows very promising results. [11]

According to one study, 29 out of 59 patients with oral leukoplakia were randomized to use a mixed tea extract orally as well as a topical tea extract. After the 6-month trial, the oral lesions had decreased in size in almost 40% of the patients treated, which was associated with a decrease in proliferation in the treatment group on histopathologic examination (P < 0. 05) [11]

5. Photodynamic Therapy (PDT)

Photodynamic therapy is a non-invasive method of treatment for head and neck tumors and premalignant lesions . [2, 15]

It is based on photo-chemical reaction, initiated by light activation of a photosensitizing drug causing tumor cell death. It requires the simultaneous presence of a photosensitizing drug (photosensitizer), oxygen, and visible light and it is a non-thermal reaction. [2, 15]

The photosensitizer is administered systemically by intravenous injection or can be topically applied. [2]

After a period to allow the photosensitizer to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug specific wavelength. [15]

Mainly, the light source consists of a portable diode laser and the light is transmitted via laser fibers to or into the tumor [10]

Intracellular activation of the photosensitizer drug results either in the production of radicals (type I mechanism) or the formation of intracellular singlet oxygen (type II mechanism), which causes cell death by vascular shut down mechanisms and intracellular oxygenation. [15]

The main advantages of PDT are:
• Photodynamic therapy is a localized therapy and it has only localized effects as the photosensitizer is selectively absorbed by the target tissues.
• Photosensitizing agents have low systemic toxicity.
• Photodynamic therapy is more economical than radiation therapy and surgical therapy for cancer patients.
• PDT is less invasive, has no long-term side effects and can be repeated many times at the same site, if needed.
• Photodynamic therapy has excellent cosmetic results and the healing process results in little or no scarring.[16]

There are several photosensitizers which have been developed and approved in time: (1) Photofrin; (2) 5-Aminolaevulinic acid (ALA); (3) Verteporfin ;(4) Foscan. [2, 10]

5-Aminolevulinic acid (ALA)- mediated photodynamic therapy (PDT) is a new therapy for the treatment of oral leukoplakia. [15]

5-Aminolevulinic acid is the only photosensitizer which can be given orally or applied topically. All other photosensitizers have to be given intravenously. [15]

A study was done to determine therapeutic response to PDT in patients with oral leukoplakia. Twelve patients were selected with lesions at a variety of intraoral sites. Patients were treated with topically applied 10% ALA and light from an argon-pumped dye laser. Irradiation was performed in several (6-8) sessions using light at 635 nm wavelength, delivering a total dose of 100 J/cm2 per session. A complete response was obtained in 10 out of 12 treated patients. One recurrence was observed during 6 months. [15]

The photodynamic therapy appears to be a feasible alternative to conventional therapy of premalignant lesions of oral cavity. [15]

At present, PDT is most successful for the superficial lesions of the epithelium such as basal cell cancer, micro invasive and intraepithelial dysplasias. The maximum depth of necrosis achieved by PDT is at around 1 cm hence it is not suitable for lesions greater than 1 cm diameter.[16]

Surgical treatment of oral leukoplakia
1. Conventional surgery- excision

Conventional surgery refers to scalpel excision of the lesion. [2]

This is followed by a primary closure or secondary healing in case of reduced mucosal defects or with a transposition of local mucosal faps or even skin graft in case of large defects. [2]

Conventional surgery may not feasible for extensive lesions or those in certain anatomical locations. [3] The associated morbidity of surgery also makes it less appealing for extensive lesions. [3]

The use of a scalpel may induce wide areas of denudated mucosa with unfavorable scarring changes and secondary functional alterations as surgical sequelae. [4]

It should be noted however that curative surgical resection has the potential to be effective as a prophylactic treatment of lesions on the tongue having a tendency to develop cancer. [4]

2. Electrocoagulation

Electrocoagulation can be used alone or as an adjuvant to scalpel surgery. [2] Electrocoagulation produces thermal damage in the underlying and surrounding tissue, which causes postoperative pain and oedema, and leads to considerable tissue scarring. Postoperative pain and oedema are also severe after cryosurgery. [2, 3]

3. Cryosurgery

Cryosurgery is a method of treatment which involves controlled tissue damage caused by low temperatures. [1] This method locally destroys lesional tissue by freezing in situ [2, 4]

- by liquid nitrogen (N) or dinitrogen dioxide (N2O2) [1]

Arnott, a British physician, was the first person to use cryosurgery in the year 1851. Initially, its use was lim-ited to the treatment of cancer of the lip and oral cavity. At present, cryosurgery has an extensive application in the treatment of both benign and malignant lesions in the head and neck region. [17]

It has several advantages including bloodless treatment, a very low incidence of secondary infections, and a relative lack of scarring and pain. [2, 4]

Furthermore, newly rebuilt epithelium is less likely to become corneous again. [1]

It can also be used for high-risk group patients like those with a pacemaker, the elderly, and those with coagulopathies. In addition, it would be the first choice in the case of multiple and extensive lesions, areas of difficult surgical access, and areas where esthetics is important. [17]

Cryosurgical effectiveness is high and ranges from 80% to 100%. The effectiveness depends on adequate freezing time and proper freezing depth. [1]

The choice of cryosurgical methods in the treatment of oral leukoplakia depends on the depth, area, and shape of the pathological lesion, as well as on access to cryosurgical equipment and operator's experience. [1]

Available cryosurgery apparatus are classified into open and closed systems. [2, 4, 17]

Closed-system cryotherapy offers a greater degree of temperature control but requires complex, delicate, and expensive equipment. It is performed by direct contact of the cryoprobe onto the lesional surface. Because of the small and flat contact area of the cryoprobe end, closed-system cryotherapy is usually suitable for treatment of uniform, smooth-surfaced oral lesions less than 1 cm in diameter. [4, 17]

Open-system cryotherapy involves directly applying the cryogen to the lesion with a cotton swab or a portable spray apparatus. It is more difficult to maintain a constant lower temperature in the lesional tissues during the whole treatment period. However, it does not need expensive equipment. Open-system cryotherapy with the spray apparatus is suitable for treatment of medium and large oral lesions with either a smooth or a rough surface. [4]

During cryotherapy the ice crystals are formed in both extracellular and intracellular fluid leading to the cellular dehydration, toxic intracellular electrolyte concentration, inhibition of enzymes, protein damage. These mechanisms associated with the thermal shock induce the vacuolization of cells, their expansion and finally their rupture. Also the vascular changes are followed by ischemic necrosis of the treated tissue and immunological responses which will produce the damage of tissue by cytotoxic immune mechanism. [2]

4. Laser surgery (excision or evaporation)

The laser surgery has been reported as most appreciated in the last 30 years. [2]

Carbon dioxide, neodymium: yttrium-aluminium garnet (Nd:YAG), argon, and potassium-titanyl-phosphate (KTP) lasers are used in the management - vaporization or excision- of oral leukoplakia. [3]

Their precision allows a conservative and site-spe-

cific, minimally invasive surgery with sterilization of the surgical area and minimal intraoperative hemorrhage. These lasers also permit a better postoperative period, with less swelling and pain and healing with minimal scarring. [4] This can be performed even for extensive lesions. [2]

Wound healing is excellent because of limited contraction; it produces satisfactory mobility of the oral mucosa and minimum oral dysfunction. [3]

Additional advantages of lasers include an optimal visualization of the surgical area, seal of lymphatic, and nerve endings which minimizes the chances for neoplastic cells seeding and the elimination of precancerous fields (dysplasia) neighboring the leukoplakia with minimal surgical morbidity. [4]

Comparing different laser techniques, CO_2 laser, neodymium: yttrium aluminum garnet (Nd:YAG) laser, and potassium-titanyl-phosphate (KTP) there are differences in recurrence rates (34.2%, 28.9%, and 17 %). [2]

The Nd:YAG laser, because of its unique characteristics (its ability to coagulate and ablate; it is not as precise a cutting tool as the CO_2 laser), has specific advantage in the treatment of large oral vascular malformations. [18]

The CO_2 laser was one of the earliest gas lasers invented by Kumar Patel of Bell Labs in 1964, and it still remains the most useful lasers in oral and maxillofacial/ head and neck surgery practice. CO_2 lasers are by far the highest power continuous wave lasers that are currently available. They are also very useful in oral surgical procedures since the energy is maximally absorbed by water in the oral tissues. [18]

The treatment of oral leukoplakia using CO_2 laser can be best obtained by ablation or vaporization of the lesion. [4]

Ablation being done at defocused mode (achieved by moving the laser away from the tissue and beyond its focal length), reduces the power and depth of penetration of the laser beam (200-400 lm per pass), limiting the destruction to the epithelium and hence resulting in lesser pain, swelling and even scarring with better regain of elastic property of the tissue. [4]

As an alternative, the CO_2 laser vaporization (ë=10.6 ìm, continuous wave, defocused) is an established procedure that has been in use for more than 35 years. This technique has been proven to be very effective. [4]

Vaporization of tissue with a defocused laser beam is, however, not entirely minimally invasive. Horch et al. have shown histologically that thermal laser energy carbonizes superficial parts of epithelium resulting in re-epithelization being delayed for more than two weeks and the possibility of healing with scarring. A delay in wound healing can also be an encumbrance for the patient. [4]

The laser evaporation technique has a disadvantage, as no tissue is available for histopathological examination. [3], which is crucial in the case of dysplasia.[1]

The CO_2 laser treatment of potential lesions is most efficacious when used in defocused mode. It may be assumed that the heat generated can also destroy deeper-lying dysplastic cells. [4]

CONCLUSION

The degree of epithelial dysplasia is mandatory for the correct choice of the treatment. In the presence of epithelial dysplasia, surgical treatment is recommended. In cases of absence of dysplasia lesion can be completely removed or not. In this case the decision should consider clinical factors such as location, size and the patient's engagement in smoking cessation and patient's cooperation.

All individuals with leukoplakia, and those who were treated for it, should be followed-up regularly, regardless of their response to topical or systemic treatment, including clinical resolution.

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