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Oral leukoplakia

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CONTENTS

Abstract

Leukoplakia is a condition of morphologically altered tissue with an increased risk of malignant transformation to squamous cell carcinoma, especially in nonhomogeneous oral leukoplakia. Since most leukoplakias are asymptomatic, treatment of oral leukoplakia is mainly aimed at preventing malignant transformation. Several treatment approaches have succeeded in achieving significant rates of clinical resolution of oral lesions, including vitamin A, retinoids and carotenoids. However, none of these treatments has shown benefit in preventing malignant transformation when compared to placebo. This article will outline drug treatments investigated so far as chemopreventive strategies in oral leukoplakia.

Introduction

Oral premalignant lesions are either white (leukoplakia) or red (erythroplakia) mucosal patches in the oral cavity or oropharynx with a high risk of malignant transformation. Oral leukoplakia is defined by the World Health Organization (WHO) as a white lesion of the oral mucosa that cannot be characterized as any other definable lesion. Thus, leukoplakia is a diagnosis of exclusion (1). Homogeneous leukoplakias exhibit a lesser degree of malignant transformation (Fig. 1) compared to nonhomogeneous leukoplakias (Fig. 2) (2).

Prevention of malignant transformation is critical due to the poor prognosis associated with oral squamous cell carcinoma, which has a survival rate at 5 years after the initial diagnosis of as little as 30% (3). At present, clinical features are the most relevant prognostic factors, although several potential markers have recently been identified to enable a more objective evaluation of the presence of epithelial dysplasia in the oral mucosa, *i.e.*, heat shock protein 70 (HSP70), nuclear factor-κ B (NF-κB) and cyclooxygenase type 2 (COX-2) enzyme (4, 5).

Oral leukoplakia is not a rare condition. Although variable among geographical areas and demographic groups, oral leukoplakia is estimated to affect around 1-5% of the general population (1). Chronic irritation of the oral tissues appears to be the major etiological factor, especially due to smoking (6, 7). Removing the source of irritation is usually the treatment of choice for oral leukoplakia. When this approach does not clear the condition or the lesion shows signs of malignant transformation, surgery is accepted as an adequate treatment. However, surgery is not a viable treatment option for extensive or multiple lesions, and since recurrence is not uncommon after surgical treatment (2, 3, 8, 9), pharmacological therapy may be a necessary strategy for some patients. Since most leukoplakias are asymptomatic, the primary objective of treatment should be to prevent the malignant transformation of the oral lesions (1). Relevant clinical studies with drug therapy are summarized in Tables I and II.

Pharmacological treatments

Vitamin A and retinoids

Randomized, controlled trials assessing the efficacy and safety of several drugs for the treatment of oral leukoplakia, including vitamin A and retinoids, have recently been reviewed (1). Results of the analysis showed that vitamin A and retinoids (isotretinoin, acitetrin) produced a small but significant benefit in terms of complete resolution of oral lesions.

Topical isotretinoin (13-*cis*-retinoic acid; 0.1% t.i.d.) (10), vitamin A (200,000 IU weekly) (11) and topical acitretin (10 mg b.i.d.) (12) did not appear to cause any adverse effects. A recently published long-term follow-up study tested the efficacy of topical therapy with 0.18% isotretinoin b.i.d. for 3 months compared to 0.05% in 40 patients. Topical 0.18% isotretinoin produced a statisti-

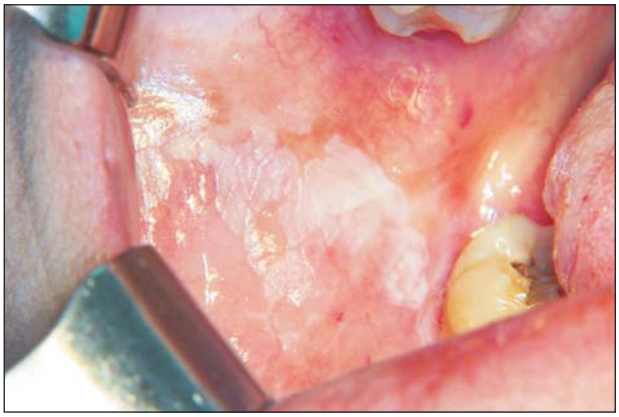

Fig. 1. Homogeneous oral leukoplakia in the buccal mucosa.

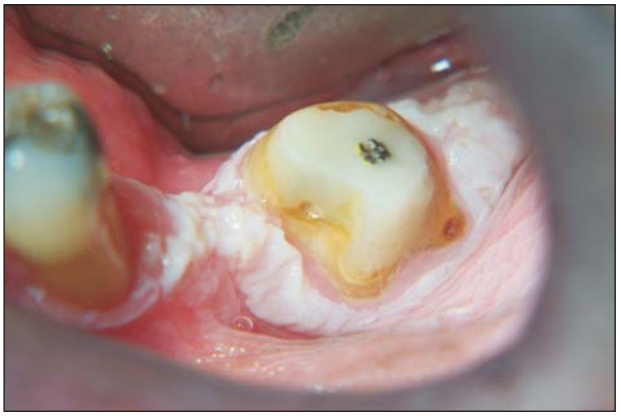

Fig. 2. Nonhomogeneous oral leukoplakia in the inferior alveolar ridge mucosa.

cally significant reduction in lesions when compared to the lower concentration ($p < 0.01$), with no associated topical or systemic adverse reactions. A group of 20 patients had a 10-year follow-up to evaluate any lesion relapse following therapy interruption, with a relapse occurring in 4 of these patients. None of the patients included in the study showed malignant progression of the lesions (13).

Two other studies assessed the use of vitamin A as a chemopreventive agent in oral leukoplakia, but despite some clinical efficacy in inducing the regression of lesions, vitamin A treatment failed to show any benefit in preventing recurrences and malignant transformation. The first trial was an open-label study using topical 0.05% vitamin A acid gel in 26 patients for a mean of 3.5 years in patients with clinical improvement and 1.5 years in those with no response (14); the second trial was a randomized, double-blind, placebo-controlled study in 160 patients receiving oral vitamin A or β-carotene for 1 year (15).

Fenretinide (4-HPR), a synthetic analogue of retinoic acid, has also been advocated for the treatment of oral leukoplakia (16). Results of a recent phase II study in 38 patients with oral leukoplakia not responding to natural retinoid treatment showed that 200 mg/day of fenretinide for 3 months was an effective therapy and induced a moderate increase in apoptosis (17). Another multicenter, controlled study evaluating the efficacy of fenretinide at preventing relapses, new lesions and carcinomas after surgical excision of oral leukoplakia showed that patients randomized to receive 200 mg/day of fenretinide for 1 year had lower relapse rates than those randomized to no pharmacological intervention. Analysis at 5-year follow-up suggested that fenretinide was well tolerated and protected against relapses and new lesions up to 19 months after randomization (18).

Carotenoids

A population-based case-control study in male Japanese patients showed that high serum levels of β-carotene were related to a low risk of oral leukoplakia, suggesting that β-carotene might be used as a chemopreventive agent for oral cancer (19). However, a randomized, controlled trial carried out in Finland in which 343 male smokers with or without oral leukoplakia were treated with β-carotene or vitamin E for 5-7 years showed that β-carotene had no effect on the appearance of precancerous lesions, despite 7-fold greater concentrations of β-carotene in the buccal mucosal cells after long-term supplementation (20). Two randomized, controlled studies assessed the efficacy of β-carotene in oral leukoplakia, either compared to vitamin A (15) or isotretinoin (21). Despite some clinical efficacy in reducing oral lesions, neither of these studies managed to show efficacy for β-carotene in the prevention of malignant progression of oral leukoplakia.

Lycopene is the most common carotenoid in the human body and is one of the most potent carotenoid antioxidants. The results of a randomized clinical study showed that patients receiving oral lycopene at doses ranging from 4 to 8 mg/day over 3-5 months had significant clinical (size and color) and histological (level of dysplasia) improvement when compared to placebo (22).

Photodynamic therapy

Photodynamic therapy (PDT) is based on the administration of photosensitizers, which are selectively retained in tumor tissues and induce cytotoxicity after light irradiation (23). δ-Aminolevulinic acid (ALA), although not a photosensitizer *per se*, has been successfully used in the diagnosis and treatment of neoplastic tissues. ALA bypasses the feedback control system in the heme biosynthetic pathway, resulting in cellular accumulation of protoporphyrin IX, an effective photosensitizer. In recent years, several studies have shown promising results with the use of topical ALA for the treatment of oral leukoplakia (24, 25). In a more recent study, researchers from the National Taiwan University treated 24 oral leukoplakia lesions with 20% ALA-PDT applied topically twice a week during a 3-8-week period. Their results revealed 8 complete remissions and 16 partial responses. Only 2 of the 8 oral leukoplakia lesions recurred 9 and 11 months

Table I: Clinical studies of vitamin A, retinoids and carotenoids in the treatment of oral leukoplakia (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Retinoids	Randomized Double-blind	Isotretinoin, 0.1% gel top. t.i.d. x 4 mo Placebo x 4 mo → Isotretinoin, 0.1% gel t.i.d. x 4 mo	10	Topical isotretinoin showed good results in the treatment of oral leukoplakia	10
	Randomized Double-blind	Vitamin A, 200,000 IU p.o./wk x 6 mo Placebo	65	Oral administration of vitamin A was significantly more effective than placebo in producing complete remission of oral leukoplakia and suppressing new lesions	11
	Randomized Double-blind	Acitretin, 10 mg x 2 p.o. x 4 wks Placebo	21	Acitretin administered as mucoadhesive tablets was effective and well tolerated in the treatment of oral leukoplakia	12
	Randomized Open	Isotretinoin, 0.05% top. b.i.d. x 3 mo Isotretinoin, 0.18% top. b.i.d. x 3 mo	40	Topical isotretinoin therapy was associated with a reduction in the aggressiveness of leukoplakia and disappearance of dysplastic phenomena, being effective in patients with highly active oral leukoplakia with dysplastic phenomena	13
	Open	Vitamin A, 0.05% gel top. q.i.d. x 1.5 y [if no response] or 3.5 y [if response]	26	Topical vitamin A showed limited efficacy in patients with oral leukoplakia. About 27% of patients achieved complete remission, but recurrence was observed in up to 40% of these patients when treatment was discontinued	14
	Randomized Open	Fenretinide, 200 mg p.o. o.d. x 27 d 1x/mo x 1 y Control	137	Fenretinide was well tolerated and effective for the prevention of relapses and new lesions during treatment in patients previously operated for oral leukoplakia	16
	Open	Fenretinide, 200 mg/d p.o. x 3 mo	38	Fenretinide was effective and induced a moderate increase in apoptosis in subjects with retinoid-resistant oral leukoplakia	17
	Randomized Open Multicenter	Fenretinide, 200 mg p.o. o.d. x 27 d 1x/mo x 1 y Control	170	Fenretinide was well tolerated and effectively prevented relapses and new lesions during and after treatment in patients operated for oral leukoplakia	18
Retinoids vs. Carotenoids	Randomized Comparative	Vitamin A, 300,000 IU p.o. 1x/wk x 1 y β-Carotene, 360 mg p.o. 1x/wk x 1 y Placebo	160	Vitamin A was more effective than β-carotene in achieving complete remission, but relapse after stopping therapy was high in all groups	15
	Randomized Open Comparative	Isotretinoin, 1.5 mg/kg/d p.o. x 3 mo → Isotretinoin, 0.5 mg/kg/d p.o. x 9 mo Isotretinoin, 1.5 mg/kg/d p.o. x 3 mo → β-Carotene, 30 mg/d p.o. x 9 mo	70	Low-dose isotretinoin was well tolerated and was more active than β-carotene for leukoplakia when preceded by high-dose isotretinoin induction therapy	21
Carotenoids	Randomized Comparative	β-Carotene, 20 mg/d p.o. x 3 y Vitamin E, 50 mg/d p.o. x 3 y β-Carotene, 20 mg/d p.o. + Vitamin E, 50 mg/d p.o. x 3 y Placebo	343	β-Carotene concentration in oral mucosal cells was 7-fold greater in subjects receiving long-term supplementation with β-carotene compared with subjects not receiving supplementation. In patients with oral leukoplakia no association was found between cellular β-carotene concentration and precancerous lesions	20
	Randomized	Lycopene, 2 mg p.o. b.i.d. x 3 mo Lycopene, 4 mg p.o. b.i.d. x 3 mo Placebo	56	Lycopene was safe and effective for the treatment of oral leukoplakia	22

after complete regression of the lesion (26). The same institution is currently investigating the use of PDT for oral leukoplakia and erythroleukoplakia in an open-label study with a projected accrual of 40 patients (27).

Calcipotriol

The vitamin D analogue calcipotriol has proven effective against several hyperproliferative conditions.

Table II: Clinical studies with other drug therapies investigated for oral leukoplakia (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
δ-ALA PDT	Open	Aminolevulinate [cream], 3-5 g top. 1x/30 min x 2 h → Argon-pumped dye laser light irradiation, 100 J/cm^2	12	Topical aminolevulinate treatment was effective in most patients with oral leukoplakia, with 42% showing a complete response and 33% a partial response	24
	Open	Aminolevulinate, 10% top. → Red laser light irradiation, 100 J/cm^2 x 6-8 sessions	12	Topical aminolevulinate in combination with photodynamic therapy produced a complete response in 10 of 12 patients with oral leukoplakia	25
	Open	Aminolevulinate, 20% top. → Photodynamic therapy over 1.5 h 1x/wk Aminolevulinate, 20% top. → Photodynamic therapy over 1.5 h 2x/wk	32	Oral verrucous hyperplasia showed complete regression after < 6 sessions of treatment with topical aminolevulinate in combination with photodynamic therapy. Oral leukoplasia showed at least a partial response after 8 twice-weekly sessions, which was more effective than treatment administered once weekly	26
Calcipotriol	Open Comparative	Calcipotriol, 50 mg/g top. b.i.d. during ≥15 min/d x 5 wks Tretinoin, 50 mg/g top. b.i.d. during ≥15 min/d x 5 wks	40	Topical calcipotriol was as effective as topical tretinoin for the treatment of oral leukoplakia	28
NSAIDs	Randomized Double-blind	Ketorolac, 0.1% oral rinse 10 ml over 30 s b.i.d. x 90 d Placebo	57	Ketorolac oral rinse and placebo were well tolerated and showed similar response rates in patients with oropharyngeal leukoplakia	31
	Multicenter Randomized	Sulindac, 150 mg p.o. b.i.d x 24 wks Placebo	66	A clinical study was initiated to evaluate the efficacy of sulindac for the treatment of premalignant oral lesions	32
	Open	Celecoxib, 400 mg b.i.d. x 3 mo → [if > 30% decrease in oral premalignant lesions] Id. x 9 mo	20	Preliminary results suggested that celecoxib was well tolerated and associated with favorable PGE_2 modulation, which was sustained in some patients with oral premalignant lesions	33
	Randomized Double-blind	Celecoxib, 100 mg p.o. b.i.d. x 12 wks Celecoxib, 200 mg p.o. b.i.d. x 12 wks Celecoxib, 400 mg p.o. b.i.d. x 12 wks Placebo	56	Treatment response to celecoxib in patients with oral premalignant lesions was not significantly different from placebo	34
Thiazolidine-diones	Open	Pioglitazone, p.o. o.d. x 12 wks	33	A phase II study was initiated to assess the safety, tolerability and efficacy of pioglitazone in patients with head and neck cancer and leukoplakia	35
	Open	Rosiglitazone, p.o. o.d. x 12 wks [if no toxicity]	25	A phase II study will assess the efficacy of rosiglitazone in preventing oral cancer in patients with oral leukoplakia	36
Tea extracts	Randomized Double-blind	Green tea extract, 0.76 g p.o. q.i.d. + Green tea extract, 10% mixture top. t.i.d. x 6 mo Placebo	28	Green tea extract showed direct protective effects in patients with oral leukoplakia, such as inhibition of cell proliferation	40
	Open	Black tea extract [1 teaspoonful], t.i.d. x 1 y	82	Black tea consumption for 1 year in the first 15 available patients showed gradual reversal of leukoplakia and a reduction of micronulei frequency and chromosomal aberrations	41
	Open	Green tea extract	40	A phase II study was initiated to evaluate the efficacy of green tea extract in oral leukoplakia	42

Continuation

Table II (Cont.): Clinical studies with other drug therapies investigated for oral leukoplakia (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Bleomycin	Randomized Double-blind	Bleomycin, 1% top. o.d. x 14 d Placebo	22	Topical bleomycin was well tolerated and could be useful for the treatment of oral leukoplakia, especially in cases of difficult surgical excision	43
	Open	Bleomycin, 1% top. o.d. x 14 d	19	Topical bleomycin applied to dysplastic oral leukoplakia lesions could prevent progression to carcinoma	44
Bowman-Birk inhibitor concentrate	Open Dose-finding	Bowman-Birk inhibitor concentrate, 100 CIU p.o. b.i.d. x 1 mo Bowman-Birk inhibitor concentrate, 266.5 CIU p.o. b.i.d. x 1 mo Bowman-Birk inhibitor concentrate, 400 CIU p.o. b.i.d. x 1 mo Bowman-Birk inhibitor concentrate, 533 CIU p.o. b.i.d. x 1 mo	32	Bowman-Birk inhibitor concentrate showed clinical activity in patients with oral leukoplakia. High pretreatment oral mucosal cell protease activity was associated with greater decreases in protease activity after Bowman-Birk inhibitor concentrate therapy	46
	Multicenter Randomized Double-blind	Bowman-Birk inhibitor concentrate, p.o. b.i.d. x 6 mo Placebo	210	A phase II study was initiated to evaluate the chemoprentive activity of Bowman-Birk inhibitor concentrate in leukoplakia	47

Calcipotriol thus represents a potential alternative for the treatment of oral hyperkeratotic lesions in cases where retinoids and carotenoids are contraindicated. Results from an open-label study revealed that topical administration of calcipotriol over 5 weeks produced complete remission of 80% of the lesions, showing similar efficacy to isotretinoin but fewer side effects (28).

Another vitamin D derivative, calcitriol, has been claimed in patent literature for the treatment of several dermatological disorders, including leukoplakia, in combination with clobetasol propionate (29, 30).

Nonsteroidal antiinflamatory drugs

Cyclooxygenase (COX) has been implicated in a number of epithelial cancers and is recognized as an important chemopreventive target. Recently, COX-2 has been identified as a molecular marker of oral tumor progression (5). Therefore, COX inhibitors such as nonsteroidal antiinflamatory drugs (NSAIDs) could be expected to help manage early oropharyngeal carcinogenesis. However, a first approach with ketorolac 0.1% oral rinse failed to demonstrate such potential benefits (31). A multicenter chemoprevention trial of sulindac, another pan-COX inhibitor, for oral leukoplakia is ongoing. Up to 60 subjects will be randomized to receive either placebo or sulindac 150 mg b.i.d. to test the efficacy, safety and molecular effects of the drug against oral premalignant lesions and tissue (32). The COX-2 inhibitor celecoxib has also been investigated in patients with oral premalignant lesions. Preliminary results of an open-label phase II clinical study in 20 patients showed that celecoxib was associated with favorable prostaglandin E_2 (PGE_2) modulation (33). Nevertheless, the recently reported clinical and histological results from a randomized, placebo-controlled trial of celecoxib in 56 subjects with oral premalignant lesions found no statistically significant differences in the response rate between placebo and active intervention (34).

Thiazolidinediones

Pioglitazone is in phase II evaluation at the National Cancer Institute (NCI) for the prevention of head and neck cancer in patients with oral leukoplakia (35). In this ongoing open-label trial, patients are scheduled to receive oral pioglitazone once daily for 12 weeks and are followed at 4, 8, 12 and 16 weeks. The primary objective of this study is to determine whether pioglitazone is able to reverse leukoplakia in patients with hyperplastic or dysplastic oral cavity or oropharyngeal leukoplakia. Similarly, a multicenter, open-label study is ongoing with the aim of studying rosiglitazone as a chemopreventive in patients with oral leukoplakia (36). With a projected accrual of 25 patients, the primary outcome measure will be the clinical response rate to oral rosiglitazone after 12 weeks of treatment. After completion of the study, patients will be followed for 1 week.

Tea extracts

The relationship between tea *(Camellia sinensis)* consumption and the incidence of human cancer has been a matter of study during the last years due to epidemiological evidence pointing to a chemoprotective role for green-yellow-orange vegetables and fruits. Green tea is prepared from fresh tea leaves that are pan-fried or steamed and dried to inactivate enzymes; biochemically, it is characterized by the presence of catechins. Black tea is prepared by crushing withered tea leaves, which are then fermented; biochemically, it is characterized by the presence of theaflavins and thearubigins (37). Studies demonstrating the chemopreventive effects of polyphenolic phytochemicals, including tea preparations and tea polyphenols, were recently reviewed (38).

Inhibitory effects of green tea on leukoplakia were suggested by *in vitro* findings for its major polyphenolic compound, (–)-epigallocatechin-3-gallate, in a human multistage carcinogenesis model of oral cancer (39). Only one randomized, placebo-controlled trial has assessed the effects of tea in oral leukoplakia. In this trial, a tea preparation comprised of a mixture of green tea extract, green tea polyphenols and tea pigments was administered both orally and topically for 6 months (40). Another study with an open-label design investigated the effects of black tea consumption for 1 year in patients with oral leukoplakia (41). Results of both trials indicated that tea produced partial regression of the lesions and a significant decrease in the micronuclei frequency and chromosomal aberrations. A phase II clinical trial sponsored by the University of Medicine and Dentistry of New Jersey is currently being conducted in order to evaluate the effects of green tea in oral leukoplakia (42).

Bleomycin

Bleomycin is a glycosylated linear nonribosomal peptide antibiotic produced by the bacterium *Streptomyces verticillus*. Bleomycin has been used for a number of years as an anticancer agent for the treatment of squamous cell carcinomas. Only one randomized, double-blind, placebo-controlled clinical trial has so far evaluated the use of topical bleomycin for the treatment of oral leukoplakia (43). The results of this study revealed that topical application of 1% bleomycin with iontophoresis for 14 consecutive days produced a significant reduction in the clinical size of the lesions and histological reduction in dysplasia compared to placebo. Nevertheless, the results of this study should be interpreted with caution due to its small sample size and relatively short follow-up period (15 months). The same authors conducted an open-label trial with bleomycin under the same treatment conditions in 19 patients with dysplastic oral leukoplakia (44). Most patients attained at least partial responses; however, after a mean follow-up of 3.4 years, lesions in 3 patients transformed to malignancies.

Bowman-Birk inhibitor concentrate

Bowman-Birk inhibitor (BBI) is an abundant protease inhibitor in soybeans with particularly strong anticarcinogenic properties. The mechanism by which Bowman-Birk inhibitor concentrate (BBIC) exerts its anticarcinogenic effect remains to be determined (45). The results of a 1-month phase IIa clinical trial revealed that the application of BBIC for the treatment of oral leukoplakia produced a 24.2% decrease in total lesion area at all doses tested (46). These results, although modest, indicate that BBIC should be investigated for chemopreventive activity in a randomized clinical trial. At present, a phase II clinical trial sponsored by the NCI is being conducted in order to evaluate the effects of BBIC in preventing cancer in patients with oral leukoplakia (47).

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