Review Article

A Review on the Management of Premalignant Lesions with Epithelial Dysplasia

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ABSTRACT

The presence of epithelial dysplasia is one of the prognostic predictors of malignant transformation rate of premalignant or potentially malignant lesions. Erythroleukoplakias, nodular leukoplakias, verruccous leukoplakias and intraepithelial carcinomas show an increasing frequency of dysplastic histological changes or aneuploidy. Medical and surgical management strategies for their treatment have shown promising results. This article is an attempt to review the management update of these advanced premalignant lesions.

Introduction

A Premalignant lesion is defined as " a morphologically altered tissue in which malignancy is more likely to occur than its normal counterpart". The histopathologic features are highly variable, ranging from hyperkeratosis and hyperplasia to atrophy and severe dysplasia. Dysplastic lesions do not have any specific clinical appearance; however, where erythroplakia is present, dysplasia is likely. Erythroleukoplakias, verrucous leukoplakias, and nodular leukoplakias show an increasing frequency of dysplastic histologic changes or aneuploidy. Carcinoma in situ is a controversial term used for severe dysplasia in which the abnormalities extend throughout the thickness of the epithelium. Top-to-bottom epithelial dysplasia, like other dysplastic lesions, has no characteristic clinical appearance, although erythroplasia often proves to be carcinoma in situ or early invasive carcinoma.

Management of these premalignant lesions include cancer chemoprevention which is defined as the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer. The success of several recent clinical trials in preventing cancer in high-risk populations suggests that chemoprevention is rational and appealing strategy

Potential molecular markers for progression of oral epithelial dysplasia to carcinoma

These include microassay technology, loss of heterozygosity, apoptosis and cell cycle alterations, aberrant DNA expressions, matrix metalloproteinases, vascular endothelial growth factors, cytokeratins, integrins, cell surface glycoproteins and growth factor

receptors. Such markers could possibly also serve as therapeutic targets for future management strategies.

REVIEW OF VARIOUS TREATMENT MODALITIES

Elimination of etiologic factors

Prohibition of smoking, removal of any sharp tooth or faulty metallic restorations etc. remains the key issue in both the prevention and management of premalignant lesions of oral mucosa.

Dietary changes

Preliminary studies have found that low dietary levels of vit C, vit A, vit E and fibres are associated with increased risk of precancerous lesions. Studies have proved that patients of oral cancer have decreased levels of beta carotene levels in their body. Therefore patients should take fruits and vegetables containing high levels of these antioxidants.

CONSERVATIVE TREATMENT

Well known antioxidants like vitamins and carotenes usually are the first line of treatment. They are defined as any substance that reduces oxidative damage caused by free radicals.

RETINOIDS

Retinoids are natural and synthetic derievatives of vitamin A . They have diverse structures, pharmacological profiles, receptor affinities, biologic activities and specific toxities. They are thought to inhibit the carcinogenic process by interacting with several classes of intranuclear retinoid acid receptors. Clinical trials involving retinoids have established the proof of principle that the use of chemical agents inhibit, stop, or even reverse the carcinogenic process of oral cancer. Hence, the retinoids have become the archetypal chemopreventive agents for oral premalignant lesions. Initial studies used naturally occurring retinoids such as retinyl palmitate, all-*trans* retinoic acid (ATRA) or 13-*cis*-retinoic acid (13-*cis*-RA). However, with the increase in the availability of synthetic retinoids, more active compounds that have lower toxicity and improved pharmacokinetics than the natural retinoids have been identified. Hong et al. reported the first successful randomized, placebo-controlled oral leukoplakia trial in 1986. This trial used high-dose 13-cis retinoic acid (13cRA) for three months and showed a major reduction in size of oral leukoplakia in 67% of patients receiving the retinoid versus 10% of patients receiving placebo ($P = 0.002$).

Stich et al. compared 100,000 IU of vitamin A twice weekly with placebo in 65 patients with oral leukoplakia from tobacco or betel nut use. Vitamin A users had higher complete remissions (57% versus 3%) and no progression of their lesions when compared with placebo (0% versus 21%).

In addition to the above-mentioned groundbreaking trials with retinoids in monotherapy regimens, retinoids have been employed in combinatorial regimes with other substances, such as interferon- and –tocopherol like in advanced lesions which are resistant to single agent retinoid therapy. Drug therapy with a synthetic, prescription form of vitamin A (known as Accutane®, isotretinoin, and 13-*cis* retinoic acid) has been reported to be more effective than treatment with 50,000 IU per day of beta-carotene. However, because of the potential toxicity of the vitamin A-like drug, it

may be preferable to treat leukoplakia with beta-carotene, which is much safer.

ISOTRETINOIN

High dose therapy with the vitamin A analogue isotretinoin has been shown to inhibit the progression of precancerous oral leukoplakias into oral cancer. The use of this drug is limited, however, by its toxicity. A drug trial was designed to determine whether, a low toxic dose of isotretoin (0.5 mg per kilogram per day) would be effective in treatment of leukoplakia in comparison to beta carotene. The findings of this study indicated that, when preceded by high-dose isotretinoin therapy, low-dose isotretinoin therapy was more effective than [beta]-carotene in the treatment of oral leukoplakia.

FENRETIMIDE

The retinamides are synthetic retinoids that can potently induce apoptosis in cancer cells via a retinoid receptor–independent mechanism in addition to having retinoid receptor–dependent effects. Researches has shown that low-dose fenretinide (200mg/dl) is clinically active and produces a small increase in apoptosis in retinoid-resistant oral leukoplakia.

SELENIUM

Epidemiologic data suggest that lower levels of selenium in the blood may contribute to an increased risk of incidence of some cancers. A study conducted in India found that supplementation with selenium during therapy resulted in significantly enhanced cell mediated immune responsiveness, as reflected in the ability of the patient's lymphocytes to respond to stimulation with mitogen, to generate cytotoxic lymphocytes, and destroy tumor cells.

BETA – CAROTENES

Beta-carotene is a naturally occurring, nontoxic carotenoid with no known toxicities. In a clinical trial of betel nut chewers with leukoplakia, supplementation with 150,000 IU of beta-carotene twice per week for six months significantly increased the remission rate compared with placebo (14.8% vs. 3.0%).In 1986, a randomized study of 13-cis retinoic acid (1 mg/kg/d) versus beta-carotene (30 mg/d) in leukoplakia was conducted. The results indicated that beta-carotene has substantial activity in oral premalignancy. Because of its lack of toxicity, it is an excellent candidate as a preventive agent for oral cancer

According to a review of clinical trials, the combination of beta-carotene and vitamin E has led to complete or partial remissions in six of eight trials studying people with leukoplakia. In one trial, administration of 50,000 IU of beta-carotene, 1 gram of vitamin C, and 800 IU of vitamin E per day for nine months led to improvement in 56% of people with leukoplakia, with stronger effects in those who also stopped using tobacco and alcohol.

LYCOPENE

Taking the antioxidant lycopene can reduce symptoms of or even reverse a mouth condition called oral leukoplakia, reports a study of *Oral Oncology* in 2004. The cancer-protective effect of tomato was attributed to its high content of the red-colored antioxidant lycopene. This study showed that taking lycopene can reverse precancerous cell changes and reduce plaques in people with oral leukoplakia. A daily dose of 8 mg was

more effective than 4 mg. (A five-ounce tomato contains approximately 8 mg of lycopene.)

Many studies have shown that the lycopene in tomato paste can be absorbed by the body more efficiently than the lycopene in raw tomatoes or tomato juice. Lycopene is also available as a nutritional supplement and in foods besides tomatoes (such as watermelon and pink grapefruit), but it is unknown whether lycopene from other sources will have the same benefit for oral leukoplakia.

NATURAL HERBS

Catechins and theaflavins, polyphenolic compounds derived from tea (*Camellia sinensis*, fam. Theaceae), have been reported to have a wide range of biological activities including prevention of tooth decay and oral cancer. In a double-blind trial, people with leukoplakia took 3 grams per day of a mixture of whole green tea, green tea polyphenols, and green tea pigments orally and also painted the mixture of the tea on their lesions three times per day for six months. Those in the green tea group had significant improvement in the healing of their lesions.

People with a precancerous condition known as oral leukoplakia can reduce their risk of oral cancer by drinking black tea, according to a preliminary study in the *Journal of Pathology, Toxicology, and Oncology*.

BLACK RASPBERRY GEL

Researches at Ohio university have reported that black raspberries are full of anthocynins (potent antioxidant that give raspberries their brown color) and they have role in silencing cancerous cells. The gel prepared appeared to be a valid means of delivering anthocynins directly to precancerous cells, since it slowed or reduced lesion progression in about two-thirds of study participants.

CHEMOTHERAPEUTIC AGENT (BLEOMYCIN)

A study evaluated the use of topical 1% bleomycin in dimethylsulfoxide for the treatment of dysplastic oral lesions. Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients. Results showed that seventy-five percent of patients had resolution of dysplasia at follow-up biopsy, with a mean improvement of two histologic grades of dysplasia after topical chemotherapy. It was concluded from the study that topical bleomycin may prevent the potential progression of leukoplakia through dysplasia to carcinoma. However close follow-up of all patients with dysplasia is required.

CYCLOOXYGENASE-2 INHIBITORS

Celecoxib, a high specific COX-2 inhibitor with minimal toxicity has already been shown to be effective in prevention of colon adenomas. The efficacy of COX-2 inhibition that was predicted on the basis of molecular biology results was confirmed in an oral cancer chemoprevention study in which dietary administration of celecoxib and nonspecific COX-2 inhibitor piroxicam reduced oral cancer incidence, the invasiveness of induced cancers and cancer associated mortality. The combination of COX-2 and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKIs) leads to inhibition of cell growth by simultaneously blocking EGFR and COX-2 pathways. The combination holds great potential foe oral cancer prevention and treatment.

ASPIRIN

Aspirin is a nonselective COX inhibitor that blocks the action of COX-1 and COX-2, in turn inhibiting prostaglandin synthesis, particularly PGE 2. Thun et al examined the relative risk of death from buccal cancers in aspirin users and found a 30% nonsignificant risk reduction in some categories of aspirin users. Other hospital based case control studies have shown that aspirin use was associated with a 25% reduction in the risk of head and neck cancer.

GENE THERAPY

Gene therapy essentially consists of introducing specific genetic material into target cells without producing toxic effects on surrounding tissues. The introduction of new genes and the activation or inactivation of others may inhibit or suppress tumor growth. This therapy can potentially attack tumor cells while respecting normal tissue. Various modalities of gene therapy to manage precancerous lesions of oral cavity include addition gene therapy, suicide gene therapy, immunotherapy, oncolytic virus therapy, inhibition of tumor angiogenesis, gene deletion therapy and antisense RNA. Most frequent vectors in gene therapy are retrovirus, adenovirus, adeno associated virus and herpes virus.

ONYX-015 is an attenuated adenovirus designed to selectively replicate in and destroy p53 mutant cells. The safety and efficacy of topical ONYX-015 application as a chemopreventive agent was studied in patients with oral dysplasia who received a mouthwash formulation held in the mouth for 30 minutes. Histologic resolution of dysplasia was seen in 7 of the 19 cases. The trial also explored the feasibility of topical administration of a chemopreventive agent in a mouthwash, the treatment of entire oral mucosa as a field, and the avoidance of systemic toxicities in a preventive strategy. The combination of gene therapy with chemotherapy (e.g. 5-fluoracil) and immunotherapy also has shown promising results obtained in the use of adenovirus to act at altered gene level (e.g. p53).

MISCELLANEOUS

A viral basis for some leukoplakia-type lesions has been suggested, as not all affected persons have the commonly identifiable risk factors of tobacco usage and/or alcohol consumption. Human papilloma viruses (HPVs), in particular high risk types 16 and 18, have been detected in up to 85% of examined leukoplakia-type lesions. However, the exact association of HPV with OED still remains unclear. At present, agents such as imiquinod are available for the treatment of cutaneous HPV infection, but are not licensed for oral topical application, hence it is not known if such an approach would be of therapeutic benefit for OED. Antifungal strategies may seem attractive for the treatment of leukoplakia as correlations between the intra-lesional presence of candida and degree of OED and between the frequency of oral yeast and likelihood of OED or SCC have also been reported. However, there is no good data indicating that topical or systemic antifungals reliably resolve leukoplakias nor lessen the risk of malignancy in the mouths of affected individuals

TREATMENTS UNDER PROGRESS

EKB-569-- family of drugs called EGFR inhibitors.

PIOGLITAZONE---- peroxisome proliferators- activated receptor inhibitor.
Ad5MV------- targets the TP53 gene.

SURGICAL MANAGEMENT

CONVENTIONAL SURGERY

Total excision is aggressively recommended when histopathologic moderate to severe dysplasia have been identified. Jon Sudbo in his prognostic study did not indicate whether standard treatment in the form of preventive excision of leukoplakia would be adequate treatment. Conceivably, local treatment in the form of surgical excision could prevent later carcinomas. In a follow-up study, he recently demonstrated that complete resection of oral leukoplakia does not prevent the development of carcinoma and that oral carcinoma arising from aneuploid leukoplakia has an aggressive clinical behaviour despite complete resection. Among 150 patients, 37 had positive resection margins after initial resection of the leukoplakia and 113 had negative margins. The percentage of positive margins was similar in the di-, tetra-, and aneuploidy groups (25%, 25%, and 22%, respectively). Thirty-two percent of the patients with negative resection margins and 30% with positive resection margins developed a carcinoma . Because of their high malignant transformation rate (70% within 3 years after diagnosis of aneuploid leukoplakia; high rate of relapses and high lethality (30% mortality rate within 3 years), aneuploid leukoplakias should be viewed as true carcinoma and treated accordingly. Although it was previously reported that rare, aggressive oral erythroplakia with aneuploidy has a high mortality risk despite complete resection, this was the first report of cancer mortality risk in patients with the far more common premalignant lesion oral leukoplakia. The failure of current treatment to avert cancer demonstrates an unmet medical need in these patients and calls for new treatments and preventive measures.

ELECTROCAUTERY AND ELECTROSURGERY

Destruction of tissue by high voltage electric current. Advantages of this technique are its ability to coagulate premalignant lesions and provide easy control of hemorrhage. However, studies have shown both limited effectiveness and predictability of this technique relative to permanent eradication of dysplastic lesions.

CRYOSURGERY

Tissue is exposed to extreme cold to produce irreversible cell damage. Cell death occurs at -20 degree Celsius. Cryo probes refrigerated by liquid nitrogen or pressurized nitrogen oxide is used. Freezing induces crystal formation leading to cell death. Cryotherapy is not considered to be a first line therapy of oral leukoplakia and related disorders, by virtue of its lack of widespread clinical availability and risk of post-operative scarring, tissue contraction and importantly the resultant inability to observe signs of clinical recurrence.

LASER

A laser is an electronic-optical device that produces coherent radiation. The term "laser" is an acronym for "Light Amplification by Stimulated Emission of Radiation". Carbon dioxide, NdYAG, and KTP laser have been employed with various vaporization or excision

techniques for the treatment of oral leukoplakia. The main advantages of laser therapy are the potential haemostatic effects and the potential for limited tissue contraction and scarring post-therapy, both of which may permit the treatment of lesions of large dimension. Laser peel is usually used to remove lesions having large surface areas. Ablation is a noncontact surgical application in which tissue is simply vaporized. Laser surgery for oral mucosal lesions has been reported to have many advantages, and it is widely used in the treatment of oral precancerous lesions. In previous studies, recurrence and malignant transformation from the lesion have occasionally been observed following laser surgery.

Recent studies with LASER have concluded that Laser excision is suitable for leukoplakia cases on non-keratinized epithelia (i.e., the tongue and buccal mucosa), while laser vaporization is suitable for the gingival cases. Management of oral leukoplakia prevents not only recurrence and malignant transformation, but also postoperative dysfunction. Another retrospective study for evaluation of the treatment results of CO2 laser evaporation for 27 cases of leukoplakia of the lip was done which concluded that selective removal of affected epithelium with minimal damage to surrounding structures is possible using CO2 laser evaporation, followed by excellent wound healing and good functional result. Treatment can be performed under local anaesthesia on an outpatient basis. The recurrence rate is low compared with the recurrence rate after surgical excision. Therefore, CO2 laser evaporation is considered a reliable and effective treatment modality for leukoplakia of the lip. Most researchers have proved laser surgery as an excellent treatment procedure.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is another option that produces local tissue necrosis with light after prior administration of a photosensitizing agent. This heals with remarkably little scarring and no cumulative toxicity. Researches have described the use of PDT with the photosensitizing agent 5-aminolevulinic acid (ALA) for premalignant and malignant lesions of the mouth and concluded that PDT using ALA for dysplasia of the mouth produces consistent epithelial necrosis with excellent healing and is a simple and effective way to manage these patients. Also recent studies have shown that oral verrucous hyperplasia and oral leukoplakia were successfully treated with biweekly topical 5-aminolevulinic acid-mediated photodynamic therapy sessions.

RADIOTHERAPY

A case of oral leukoplakia reported in Japan in 2001, present on the right buccal mucosa of a 80 year old male was treated by laser excision four times and had been medicated by vitamin A for 4 years before radiation therapy. However, leukoplakia often recurred with pain, so radiation therapy was tried in this case. Total delivered irradiated dose was 40 Gy/20 fr/32 days. 3 years and 7 months after radiation therapy, neither recurrence nor malignant transformation occurred, and no late radiation complication existed. Radiation therapy was effective in this case for the purpose of pain relief and diminution of the lesion, so if patient is elderly, radiation therapy is thought to be a useful

modality for treating recurrent oral leukoplakia.

Conclusion

The field of oral precancerous lesions management remains an exciting and challenging area of research. Although progress has been made, this field is still in earliest stages of development and remains investigational. We are nowhere near the ultimate desired goal of possessing safe and effective preventing agents that can easily be given to the population at high risk for head and neck cancer. The next generation of chemoprevention trials will involve novel, molecular targeted agents in patients stratified based on risk factors and clearly defined biomarkers.

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