

# MANAGEMENT OF POTENTIALLY MALIGNANT DISORDERS OF ORAL CAVITY: ROLE OF MEDICAL THERAPIES

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## ABSTRACT:

Oral premalignant lesions and early stage malignancies often arise as subtle lesions and require an alert clinician with a high index of suspicion, especially if any of the risk factors are present. Presence of a precursor [pre-malignant] lesion subsequently developing into (OSCCA) is well established. *Potentially Malignant Disorders* is defined by WHO 2005 as the risk of malignancy being present in a lesion or condition either at time of initial diagnosis or at a future date. This definition warrants for targeted management of these lesions and among the diversities of available treatment options selection of one becomes a critical question. This article reviews the role of various medical therapies in the management of these lesions.

**Key words:** Potentially Malignant Disorders, Antioxidants.



## INTRODUCTION:

In developing nations like India oral health is often ignored. This reduces the natural benefit of identifying a serious problem in its inception. The condition then flourishes and takes devastating forms.

It is now known that even the clinically 'normal' appearing mucosa in a patient harboring a precancerous lesion may have

dysplasia on the contra lateral anatomic site or molecular aberrations in other oral mucosal sites suggestive of a pathway to malignant transformation, and that cancer could subsequently arise in apparently normal tissue.<sup>[1]</sup>

In a recently held WHO workshop it has been recommended to abandon the distinction between potentially malignant lesions and potentially malignant

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conditions and to use the term “Potentially Malignant Disorders” instead.<sup>[2]</sup>

Owing to the seriousness associated with these disorders any indication of their presence in the oral cavity shouldn't be overlooked. Managing these disorders efficiently requires a well aware clinician who is informed about the pros and cons of prevalent treatment modalities and can select the best possible option.

Recently the focus is shifting from surgical towards medical therapy. In this article we are reviewing the currently available medical aids, which are said to be effective in handling these disorders.

### Need to Treat??

Waldron and Shafer examined 3256 biopsy specimens from intraoral white lesions. They determined that 19.9% showed some degree of epithelial dysplasia, and 3.1% showed a frankly invasive tumor. About 5-18% of epithelial dysplasias become malignant.<sup>[3]</sup>

Oral leukoplakia has an annual malignant transformation rate of 0.1% to 17%.<sup>[4]</sup> The malignant transformation rate of oral leukoplakia is between 3.6% and 17.5%.<sup>[5]</sup>

Proliferative verrucous leukoplakia, has a high rate of malignant transformation (70.3%) to verrucous carcinoma or squamous cell carcinoma.<sup>[5]</sup>

A greater risk of malignant change in an epithelial dysplasia has been associated with the following factors.<sup>[4]</sup>

(1) Erythroplakia within a leukoplakia,

- (2) A proliferative verrucous appearance,
- (3) Location at a high-risk anatomic site such as the tongue or floor of mouth,
- (4) The presence of multiple lesions, and, paradoxically,
- (5) A history of not smoking cigarettes.

### Treatment Options:

First order of treatment must include stabilization of the mouth (treat for dryness, and fungal infection). Insist on the importance of good oral hygiene, and good nutrition.

### Role of Antioxidants in Treatment:

It is increasingly proposed that reactive oxygen species (ROS) and reactive nitrogen species (RNS) play a key role in human cancer development, especially as evidence is growing that antioxidants may prevent or delay the onset of some types of cancer<sup>[6]</sup>.

Epidemiological studies show that a high intake of antioxidant rich foods is inversely related to cancer risk<sup>[7]</sup>.

Experimental studies show that antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread, suggesting a potential role for antioxidants as adjuvant in cancer therapy<sup>[7]</sup>.

Antioxidants also show promise in cancer therapy by their palliative action, reducing

painful side effects associated with treatment<sup>[7]</sup>.

### **Retinoic Acid (Vitamin A) 13-cis-retinoic acid (13-cRA):**

WK Hong *et al*<sup>8</sup> did a randomized controlled trial at M.D. Anderson Hospital in Houston, in which they followed 44 patients with oral leukoplakias who were treated with 1-2 mg/kg/day of 13-cRA for 3 months; 32 nearly 67% of the patients had more than a 50% reduction in lesion size, but 79% experienced a variety of side effects.

Other studies<sup>[9,10]</sup> have noted that lowering the 13-cRA dose reduced the incidence and severity of side effects, but there have been numerous reports of recurrence after discontinuation.

A rise in serum triglycerides has also been reported with use of 13-cRA. Further an issue not addressed by the advocates of 13cRA was the teratogenicity of retinoic acid.

Results of preliminary trials of low-dose maintenance therapy using 13cRA are encouraging, though follow-up to date is limited

### **Carotenoids:**

The 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<sup>[4]</sup>. The use of beta-carotene has been recommended in order to prevent OL and possibly oral cancer.

Trials using b-carotene demonstrated reductions (up to 71%) in the occurrence of oral leukoplakia and mucosal dysplasia to a much lesser degree than that observed with 13cRA<sup>11-13</sup>. The percentage of patients with clinical resolution ranged from 4% to 54%, with dosages regimes from 20 to 90mg/day of beta-carotene in time periods from 3 to 12 months<sup>[4]</sup>.

It is virtually devoid of adverse reactions, thus results from trails evaluating the effect of low dose maintenance therapy of b-carotene would soon resolve the confusion about its efficacy.

### **Lycopene:**

Lycopene has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent. Lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism<sup>[4]</sup>.

The serum levels of lycopene and beta-carotene, among the 38 men suffering from OL, were significantly lower than those of the control group ( $P < 0.005$ ).

M. Singh *et al*<sup>[14]</sup> and J.M. Zakrzewska *et al*<sup>[15]</sup> from their RCT on 58 patients concluded that oral lycopene brings about histological changes of significant degree in patients with leukoplakia. Follow-up was short (3 months and 5months respectively) thus results are indicative rather than conclusive.

Lycopene poses as a potent option for controlling potentially malignant disorders but support is required.

#### **L-Ascorbic Acid (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 [4].

L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day [4].

It has been observed that individuals having serum levels of L-AA < 25µmol/l are more prone to develop OPMLD than compared with those having normal L-AA level<sup>16</sup>, another study in which 24 OPMLD patients were treated with an association of beta-carotene, vitamin E, and L-AA, and an increase was observed in the reversion of oral mucosa dysplasia. In 97.5% of patients, dysplasia were diminished by use of antioxidant combinations. The reversion of the oral mucosa dysplastic changes was more evident in the patients using antioxidative vitamins that stopped smoking and ingestion of alcohol [4].

#### **Fenretinide.(4-HPR):**

N-(4-hydroxyphenyl) retinamide is a vitamin A analogue.

S.M. Lippman et al [17] in a phase II trial dispensed 4-HPR (200 mg/day) for 3 months in OL patients who had not

responded (“de novo” resistance) or who had responded and then relapsed (acquired resistance) to the previous treatment with natural retinoids. Of 35 patients with retinoid-resistant OL, no patient had complete responses and 12 (34.3%) had partial responses to 4-HPR. Nine patients had clinical responses within 9 months of stopping 4-HPR. Toxicity was minimal and compliance was excellent. Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of 12 patients.

#### **Opposition to antioxidant therapy??**

Question arises whether antioxidants that protect normal cells from acute and long-term free radical damage may afford the same protection to tumor cells and hinder the overall outcome of cancer therapy [7].

#### **CONCLUSION:**

Treatment of lesions with low grade dysplasia is always been a controversy. Low grade dysplasia might regress by itself or can progress to malignant stages. Path which they will take is uncertain, thus ignoring them poses a degree of risk.

Another school of thought is tempering a rather quiescent lesion might provoke in it malignant changes and force it to progress towards malignancy.

Mortality rates for oral cancer have not changed in spite of the professional awareness of precancerous lesions, and their potential risk of becoming malignant. Moreover, these lesions present to us the possibility of observable

changes in the oral mucosa weeks and months prior to the onset of cancer.

Because the survival rate is directly related to the stage of malignancy at the time of diagnosis, prevention and early detection are vital to decrease the incidence and improve the survival odds of individuals who develop the disease.

P. Holmstrup *et al.* [18] from their study have shown that surgical intervention does not appear to prevent oral premalignant lesions from developing malignancy. The only significant factors associated with malignant transformation are clinical type of leukoplakia and size of the lesion. They call for the need of different modalities to attend to the cause and control its progression.

Nonsurgical treatment may also be considered for the management of OL. This modality offers minimal adverse effects to patients, especially for patients with widespread OL that involves a large area of the oral mucosa or patients with medical problems and, consequently, high surgical risks. Additionally, potential advantages of the nonsurgical treatment of OL include easy application that does not require treatment at a medical center and relative low cost.<sup>[3]</sup>

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In a Cochrane review [19,20] which included six RCTs, Vitamin A and retinoids were tested in four RCTs; the other agents tested were bleomycin, mixed tea, and beta carotene. Malignant transformation was recorded in just two studies: none of the treatments tested showed a benefit when compared with placebo. Treatment with beta carotene and vitamin A or retinoids was associated with better rates of clinical remission, compared with placebo or absence of treatment. Whenever reported, a high rate of relapse was a common finding. Side effects of variable severity were often described; however, interventions were well accepted by patients since drop-out rates were similar between treatment and control groups.

To date, in conclusion, there is no evidence of effective treatment in preventing malignant transformation of leukoplakia. Treatments may be effective in the resolution of lesion; however, relapses and adverse effects are common.

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