



Review

Topical agents for oral cancer chemoprevention: A systematic review of the literature



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ARTICLE INFO

Article history:

Received 29 October 2016

Received in revised form 12 February 2017

Accepted 20 February 2017

Keywords:

Administration, topical
Head and neck neoplasms
Leukoplakia, oral
Mouth neoplasms
Retinoids
Level of Evidence: 2a

ABSTRACT

Objectives/hypothesis: We review the use of topical chemoprevention agents in patients with oral potentially malignant disorders (PMD).

Methods: A systematic review of studies on topical chemoprevention agents for oral PMD from 1946 to November 2016 was conducted using the MEDLINE database, Embase, and Cochrane Library. Data were extracted and analyzed from selected studies including study type, sample size, demographics, treatment length, response rate, follow-up time, adverse effects, and recurrence.

Results: Of 108 studies, twenty-four, representing 679 cases met the inclusion criteria. The clinical lesions evaluated included oral leukoplakia, erythroplakia (OEL), verrucous hyperplasia (OVH), oral lichen planus, larynx squamous cell carcinoma, and oral squamous cell carcinoma (OSCC). The mean complete response rate for topical retinoid therapy was 32%. The mean complete response rate for 1% bleomycin therapy and 0.5% bleomycin was 40.2% and 25%, respectively. The complete response rate of OVH, OEL, and OSCC to photodynamic therapy ranged from 66.7% to 100%.

Conclusion: There are a paucity of data examining topical treatment of oral PMDs. However, the use of topical agents among patients with oral lesions may be a viable complement or even alternative to traditional surgery, radiation, or systemic chemotherapy, with the advantage of reducing systemic side effects and sparing important anatomic structures. This study of 679 cases represents the largest pooled sample size to date, and the preliminary studies in this systematic review provide support for further inquiry.

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Introduction

The global burden of oral squamous cell carcinoma (OSCC) continues to increase with the sustained high prevalence of common risk factors (e.g., tobacco smoking and alcohol) [1]. It frequently confers a poor prognosis, with patients commonly succumbing to aggressive locoregional recurrences or second primary tumors. Current therapeutic management of oral dysplasia and potentially

malignant disorders (PMDs) includes surgery, radiation therapy, and/or systemic chemotherapy; however, this malignancy remains difficult to treat. Of note, local recurrence following surgical management of oral lesions is reported in up to 20% of patients [2], which may be due to field cancerization of the oral cavity, where covert neoplastic progenitor cells persist outside the margins of the excision. Radiation therapy and systemic chemotherapy to treat these localized lesions have other significant disadvantages, such as bone marrow depletion and systemic toxicity.

Oral squamous cell carcinoma is the endpoint of the accumulation of genetic alterations that facilitate a transition from phenotypically normal cells to varying grades of dysplasia that eventually develop into invasive disease. Since OSCC is typically a long-term process, chemoprevention strategies can be developed to arrest or reverse this transition long before malignancy occurs.

Abbreviations: OEL, erythroplakia; OVH, verrucous hyperplasia; OSCC, oral squamous cell carcinoma.

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Chemoprevention is a low-risk strategy to inhibit the process of carcinogenesis or prevent the recurrence to malignancy. Since a majority of OSCCs are maladies that progresses from clinically-detectable precursor lesions, they are ideally suited for early non-invasive interventions. Thus, site-directed chemoprevention approaches may represent a management alternative for patients with oral PMDs.

There are a variety of advantages provided by topical therapies. One major advantage of using topical agents for PMD is the ability to provide high local and low total systemic doses to minimize toxicity. Another potential advantage is that chemopreventive agents can be applied beyond the clinical margins of the lesion to address the likely field cancerization of the oral mucosae. Patients have also articulated the psychological comfort of knowing they are actively participating in their treatment, especially in the interim between diagnosis and surgical or radiological intervention [3].

Initial studies using topical retinoids [4–9], bleomycin [10–14], adenovirus [15], cyclooxygenase (COX) inhibitors [16], photodynamic therapy [17–24], and phytochemical-enriched products [25–27] on oral lesions have been reported in the literature, and topical therapies for oral PMD remains an avid and promising field of scholarly inquiry. Thus the purpose of this systematic review was to explore whether topical agents resulted in clinical reduction in lesions compared with placebo or no treatment in patients with oral potentially malignant disease.

Methods

This review was based on a comprehensive search on MEDLINE Ovid (1946 to 30 November 2016), Embase Ovid (1980 to 30 November 2016), and Cochrane Library using medical subject heading (MeSH) terms related to topical chemoprevention of oral PMDs. The inclusion criteria were studies published from 1946 to November 2016 on topical chemoprevention for oral leukoplakia, erythroplakia, verrucous hyperplasia, oral lichen planus, larynx squamous cell carcinoma, and/or oral squamous cell carcinoma (OSCC) in humans. The exclusion criteria included non-human studies, review articles, and non-English literature. Table 1 and Fig. 1 detail the search strategy and study inclusion process. Patient information, including demographics, treatment response, recurrence, and follow-up time where reported, were extracted.

Results

The literature search yielded 108 abstracts and titles (Fig. 1). No systematic reviews evaluating topical chemoprevention in PMD were identified in the literature. Twenty-four studies met inclusion. In total, 679 cases of potentially malignant disorders (leukoplakia, $n = 446$; erythroplakia, $n = 92$; verrucous hyperplasia, $n = 108$; oral lichen planus, $n = 2$); larynx squamous cell carcinoma, $n = 10$, and/or OSCC ($n = 21$) were identified. A summary of these studies is presented in Table 2.

We assessed risk of bias in studies by using the Cochrane tool. We judged six studies to be at low risk of bias, seventeen at unclear risk and one at high risk. We assessed the overall quality of the evidence by using standardized criteria (Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE)). In general, we judged the overall quality of the evidence to be moderate, so findings are uncertain and further research is needed.

Patient characteristics

The available patient-level data for the six studies evaluating topical retinoid therapy is organized in Table 3. In total, 115

Table 1
Search strategy.

Step	Search term	Articles
11	9 and 10	108
10	topical.mp. [mp = title, abstract, full text, caption text]	141,207
9	7 and 8	517
8	chemoprevention.mp. [mp = title, abstract, full text, caption text]	10,453
7	1 or 2 or 3 or 4 or 5 or 6	14,251
6	oral cancer.mp. [mp = title, abstract, full text, caption text]	7039
5	oral leukoplakia.mp. [mp = title, abstract, full text, caption text]	1000
4	oral verrucous hyperplasia.mp. [mp = title, abstract, full text, caption text]	150
3	oral erythroplakia.mp. [mp = title, abstract, full text, caption text]	25
2	(Head and neck squamous cell carcinoma).mp. [mp = title, abstract, full text, caption text]	5144
1	oral squamous cell carcinoma.mp. [mp = title, abstract, full text, caption text]	4045

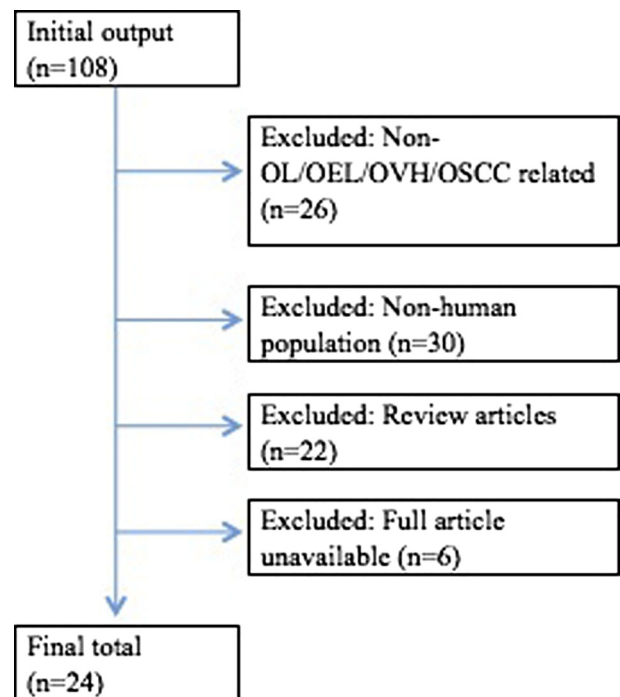


Fig. 1. Search algorithm employed.

patients received topical retinoids. The age of patients was reported in three of the six studies with a mean of 59.02 and a range of 35–81 years. Of the studies that reported gender, 64% of the patients were male.

Five studies investigated topical bleomycin for the treatment of oral leukoplakia. The aggregate data for these 69 patients are presented in Table 4. Four of the five studies reported the age of the patients with an age range of 25–82 years. In the four (of five) studies that reported gender, 51% were male.

One study in this review (Table 5) examined the use of adenovirus for treatment of oral leukoplakia, with a total of 22 patients with a diagnosis of oral leukoplakia or erythroplakia. A median age of 53 was reported in this study with a range from 29 to 80 years. Thirty-seven percent of the patients were male. Additionally, Table 5 includes a prospective controlled study investigating the use of COX inhibitors in 57 patients with oral leukoplakia [16].

The efficacy of photodynamic therapy was examined in eight studies, comprising a total of 364 cases of oral leukoplakia, ery-

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