SYSTEMATIC REVIEW

Chemoprevention of oral cancer in leukoplakia patients: A systematic review and meta-analysis

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Abstract

The systematic review and meta-analysis of published randomised controlled trials (RCTs) was conducted to review the effectiveness of current chemopreventive agents in the treatment of oral leukoplakia lesions (OPLs) and prevention of their progression to oral cancer. Material was identified through a retrospective literature search of the electronic PubMed database, Embase and Cochrane Library between 2008 and 2016.Eight RCTs were included for systematic review. The pooled estimate showed a 14% greater chance of responding for those randomised to interventions compared with placebo (Risk Ratio [RR] 1.14, 95% confidence interval [CI] 0.72 to 1.81). The CI from individual studies overlapped. The results suggested that there were no significant differences in comparing clinical responses between chemopreventive agents with placebo in treatment of OPLs. It is time to investigate new agents for oral cancer chemoprevention.

Keywords: Chemopreventive, Clinical response, Oral cancer, Oral premalignant lesions.

Introduction

Oral leukoplakia is the most common premalignant lesion in oral cavity and is associated with the development of oral cancer. Chemopreventive agents are used to suppress, reduce or prevent the progression of carcinogenesis. Patients with oral leukoplakia or postoperative oral cancer patients for prevention of secondary tumours are considered the best target population for oral cancer chemoprevention because a large proportion of oral cancers are associated with the preceding of longstanding oral leukoplakia.[1,2] Promising chemopreventive agents are needed as a treatment option for oral leukoplakia lesion (OPL), especially in elderly people who may have difficulties undergoing extensive surgeries or in lesions such as proliferative verrucous leukoplakia (PVL). So far, chemopreventive agents which have been tested in clinical trials for oral pre-cancer lesions include vitamin A, isotretinoin (13-cis retinoic acid), beta-carotene, cyclooxygenase-2 (COX-2), bowman-brick inhibitor concentration, erlotinib, green tea extract, freeze-dried black raspberry (BRB) and special medicinal herbs. In recent years, several studies were performed to test the effectiveness of chemopreventive agents in treatment of OPLs.[3-12] However, we find that the majority of the literature did not describe statistically significant differences in comparison with chemopreventive agents. In this paper, we carry out a systematic review and meta-analysis of published randomised controlled trials (RCTs) to review the effectiveness of current chemopreventive agents in treatment of oral premalignant lesions and prevention of their progression to oral cancer.

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Methods

References for this review were identified through a retrospective literature search of the electronic PubMed database, Embase, Cochrane Library between 2008 and 2016. The following key words and their combination were used in compiling the search: chemopreventive, clinical response, oral cancer and oral premalignant lesions. The electronic databases were last searched on April 29, 2016.

RCTs investigating the effectiveness of chemopreventive agents for patients with premalignant lesions, leukoplakia or erythroplakia were included. Studies investigating the preventive effects of agents for health subjects were excluded. Interventions were chemopreventive agents such as vitamin A, isotretinoin (13-cis retinoic acid), beta-carotene, COX-2, bowman-brick inhibitor concentration, erlotinib, green tea extract, BRBs and ZengShengPing, a mixture of medicinal herbs.

Main outcome measures included clinical response, change in lesion area and histological responses. Secondary outcome measures included adverse events, cancer-free survival rates, likelihood of malignant transformation and loss of heterozygosity. Clinical response used in the current meta-analysis is the overall response which is the sum of complete response (CR: regressed completely) and partial response (PR: 50% or more reduction insize).

One of the two investigators did the data extraction and

the other examined the results, and a consensus was reached. The outcomes in patients at the end of follow-up after treatments were reviewed. We extracted the following data from the eligible studies: general characteristics (subject, age, gender, location); methodology (type of study, sequence generation, masking or blinding, incomplete outcome data and other sources of bias); interventions and control groups; outcomes and statistics methods.

One investigator evaluated the quality of each study using Jadadscale.[13] The other investigator examined the results, and a consensus was reached. The Jadad score is obtained from a possible 5-point scale; high scores indicating high quality, by yes/no answers to question for randomisation and blinding, and one question evaluating the reporting of patient withdrawals and dropouts.

The meta-analysis was performed with the Comprehensive Meta-Analysis V3. For dichotomous data in the current study, rate ratio or relative risk (RR) was used for effect statistics of RCTs. Statistical heterogeneity was tested by chi-square test[14] for each outcome, with a significance set at $p<0.10$. Insignificance indicated that the results of the different trials were similar ($p>=0.1$, $I2<=50\%$). Individual and pooled results were illustrated by point estimates and 95% confidence intervals (CIs).

Results

A total of 96 abstracts from the databases were retrieved, 71(74%) of which were excluded based on their titles and abstracts. Further 17(18%) trials were excluded as 11(11.5%) did not meet inclusion criterion, and data was not provided in 6(6.25%). Only 8(8.33%) RCTs[3-10] recruiting 689 subjects were included, and 4(50%) of which[3,5,7,8] were used for meta-analysis.

Characteristics of RCTs included in the current review were noted (Table-1). Six (75%) studies[3-5,7,9,10] were performed in USA followed by 2(25%)[6,8] in Asia. The age of patients ranged from 23 to 90 years. The percentage of male patients ranged from 31% to 67% and the time to do the test ranged from 3 months to 1 year.

In 4(50%) of the RCTs included in the systematic review, the investigators described the method for the sequence generation.[3,5,6,8] Six (75%) of the studies were double-blinding.[3,5,7-10] Six (75%) of the studies described the data of missing patients. Some studies reported shortcoming or challenge of the studies, such as small number of cases enrolled and low compliance of the subjects,[8] inter-patient variation[9] and long-time duration between trial initiation and completion[7] (Table-2).

Five (62.5%) studies reported clinical responses of chemopreventive agents[3-5,7,8] to OPLs. Due to the small number of studies and heterogeneity between papers, it was only possible to conduct a meta-analysis for the

Table-1: Characteristics of RCTS.

First author	Subject	Eligible participants	Age (years) (Median, range)	Sex% male	Location	Intervention	Measurement	Time
William 2016[10]	150	Oral leukoplakia	57/57 (†)	56/57 (†)	USA	Erlotinib	Oral cancer-free survival (CFS)	1 year
Mallery 2014[9]	40	Premalignant lesions	57.7± 2.9/ 62.2 ±1.8 (**, †)	50/ 31.8 (†)	USA	Freeze-dried black raspberry (BRB)	Histologic grade, clinical size and loss of heterozygosity	3 months
Nagao 2015[8]	46	Leukoplakia	65.9± 8.7/64.8± 10.0 (**, †)	54	Japan	Beta-carotene	Clinical response (CR+ PR), likelihood of malignant transformation	1 year
Armstrong 2013[7]	89	Leukoplakia, erythroplakia	61.8 (29- 82)	64	USA	Bowman-Birk inhibitor concentrate	Clinical response (CR+ PR), change in lesion area	6 months
Sun 2010[6]	112	Oral leukoplakia	44.4± 11.8/ 52.9 ±10.4 (**, †)	79.3/ 45.8 (†)	China	ZengShengPing (a mixture of medicinal herbs)	Oral lesion size	8-12 months
Tsao 2009[5]	41	Premalignant lesions	57 (33- 76)	46.3	USA	Green tea extract	Clinical response (CR+ PR), histologic response	12 weeks
Papadimitrako-poulou 2009[4]	162	Premalignant lesions	56 (23- 90)	52.5	USA	Isotretinoin (13-cis retinoic acie), retinyl palmitate (RP), RP plus beta-carotene (BC)	Clinical response (CR+ PR), histologic response, cancer-free survival rates	3 months
Papadimitrako-poulou 2008[3]	49	Premalignant lesions	59.2/62.0 (34- 84) (†); 59.2/62.9 (34- 84) (†)	56/35 (†); 56/67 (†)	USA	Cyclooxygenase-2 (COX-2) inhibitor	Clinical response (CR+ PR), adverse events	12 weeks

**Mean Age ± SD; †Control/test.

Table-2: Evaluation of the quality of RCTs.

First author	Sequence generation	Double-blinded	Withdrawals	Jadad score (0- 5)
William 2016[10]	Adequate	Adequate	DS	5
Mallery 2014[9]	UA	Adequate	UA	2
Nagao 2015[8]	Adequate	Adequate	DS	5
Armstrong 2013[7]	Adequate	Adequate	UA	4
Sun 2010[6]	UA	NA	DS	2
Tsao 2009[5]	Adequate	Adequate	DS	5
Papadimitrakopoulou 2009[4]	UA	NA	DS	2
Papadimitrakopoulou 2008[3]	UA	Adequate	DS	4

UA, unclear; DS, described; NA, not available.

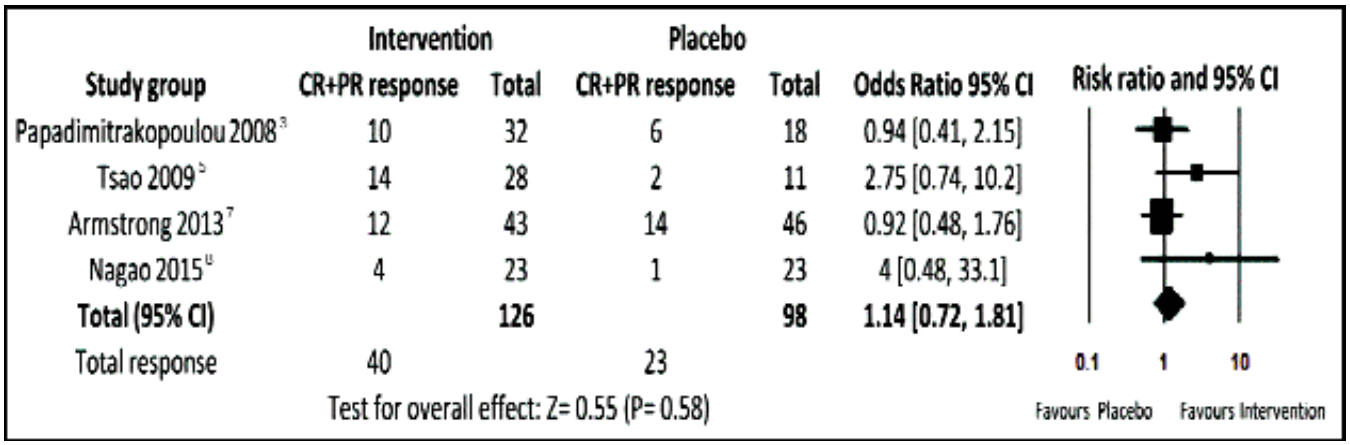

Figure: Forest plot of comparison: intervention versus placebo, outcome OPLs clinical response.

comparison of intervention versus placebo. As a result, 4(50%) studies with[3,5,7,8] 225 subjects with dichotomous data were used to do meta-analysis. The result of forest plot of comparison was also compiled (Figure). The pooled estimate showed a 14% greater chance of responding for those randomised to interventions compared to placebo (RR: 1.14; 95% CI: 0.72 to 1.81). There was no evidence of meaningful heterogeneity in this meta-analysis: I^2 was 0%, the chi^2 test for heterogeneity was not significant and the confidence intervals from individual studies overlapped. The results indicated that no statistically significant differences were found in comparing clinical responses to placebo.

Discussion

It is believed that there is an unknown carcinogen that condemns the entire oral mucosa toward malignant progression. Environmental carcinogens, including tobacco and alcohol, are recognised as the cause of epithelial field cancerisation. Also, COX-2 is reported and over-expressed in tumours.[15] These results have motivated decades of research in oral cancer prevention. COX-2-inhibiting agents have been shown to protect against colon, mammary, and oral cancer in experimental animals, and possible colorectal cancer in humans.[16] Other nature-sourced agents such as vitamin A and beta-carotene (BC) all produced significantly more objective responses than did placebo in randomised studies in oral leukoplakia patients.[17] Green tea extract (GTE) contains high amounts of polyphenols, including epigallocatechin 3-gallate (EGCG), which inhibits carcinogenesis in preclinical models.[18] Asian and other epidemiological studies have suggested a potential protective effect of green tea against epithelial malignancies.[19] It was also shown in a preclinical study that ZengShengPing (ZSP), a herbal mixture, inhibited inflammation and inflammation-associated carcinogenesis in animal models.[6] Clinical trials confirmed that oral intake of ZSP had significant chemopreventive effects on oesophageal and bronchial dysplasia. BRBs contain chemopreventive-rich composition, including anthocyanins, ellagic acid, ferulic acid, coumaric acid

and quercetin, phytosterols in addition to folic acid and selenium. Pilot clinical trial results showed that topical application of BRB gel significantly reduced loss of heterozygosity in oral intraepithelial neoplasia (OIN) lesions, modulated epithelial gene expression and significantly reduced OIN levels of COX-2.[20] Bowman Birk Inhibitor (BBI) is a serine protease inhibitor isolated from soybeans and in vitro and in vivo studies demonstrated its anticarcinogenic activity in a number of animal model systems and human trials.[21,24] In a recent study, erlotinib which targeting epidermal growth factor receptor (EGFR), was used to study its prevention effect on oral cancer. EGFR plays a critical role in oral epithelial carcinogenesis. Erlotinib have demonstrated modest activity against invasive head and neck squamous cell carcinomas,[25,26] lung carcinoma[29] and esophageal squamous cell carcinoma.[28]

However, this systematic review compared the RCTs studying the effectiveness of chemopreventive in treatment of OPLs in human, with the results showing that no statistically significant differences were found in comparing clinical responses with placebo. In the work reported by Papadimitrakopoulou et al,[4] whether retinylpalmitate (RP) alone or plus BC would be as effective and less toxic than low-dose 13cRA in treating OPLs and reducing the risk of oral cancer were investigated.[4] The 5-year oral cancer-free survival rates were measured when any of squamous cell carcinoma of the oral cavity was diagnosed. As a result, there was no significant association between 3-month OPL response and subsequent oral cancer development (p=0.072) and all the treatments failed to show significant efficacies in treating OPLs.[4] Nagao et al. also investigated the use of low-dose BC combined with vitamin C supplements as the treatment to prevent the malignant transformation to oral cancer.[8] The likelihood of malignant transformation during a 5-year follow-up period was measured. The results indicated that the treatment of BC (10 mg/day) and vitamin C were nether effective for clinical remission, nor for protection against the development of cancer.[8] William et al. tested if erlotinib (epidermal growth factor receptor inhibitor) would reduce oral cancer development in patients with OPLs.[10] The main outcome measure was oral cancer-free survival. However, erlotinib did not improve oral cancer-free survival in high-risk patients with OPLs.[10]

Conclusion

The systematic review suggested no statistically significant differences in comparing the effectiveness of current chemopreventive agents with placebo. It is time to investigate new agents for oral cancer chemoprevention.

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