INPLASY PROTOCOL

To cite: Wang et al. Traditional Chinese medicine for oral squamous cell carcinoma: A Bayesian network meta-analysis protocol. Inplasy protocol 202090082. doi: 10.37766/inplasy2020.9.0082

Received: 23 September 2020

Published: 23 September 2020

Corresponding author:
Jing Wang

lcsrmyywj@163.com

Author Affiliation:
Department of Stomatology, Liaocheng People's Hospital; Medical College of Liaocheng University.

Support: **2016ZRA15065.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
The authors declare that they have no competing interests.

Traditional Chinese medicine for oral squamous cell carcinoma: A Bayesian network meta-analysis protocol

Wang, D[1]; Duan, XJ[2]; Zhang, YH[3]; Meng, Z[4]; Wang, J[5].

Review question / Objective: **Which traditional Chinese preparation is more effective for the treatment of patients with oral squamous cell carcinoma (OSCC)?**
Condition being studied: **Traditional Chinese medicine, oral squamous cell carcinoma, efficacy and safety.**
Information sources: **Electronic databases including relevant RCTs, quasi-RCTs and high-quality prospective cohort studies were searched from Medline, PubMed, Cochrane Library, Google Scholar, Excerpt Medica Database (Embase), Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJD), Chinese Biomedical Literature Database (CBM) and Wanfang Database will be systematically searched for eligible studies from their inception to September 2020. Language is limited with English and Chinese.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 September 2020 and was last updated on 23 September 2020 (registration number INPLASY202090082).

INTRODUCTION

Review question / Objective: **Which traditional Chinese preparation is more effective for the treatment of patients with oral squamous cell carcinoma (OSCC)?**

Rationale: **Traditional Chinese medicine (TCM) is frequently used for malignant tumors in China, but in clinical practice, most practitioners choose appropriate TCM based on personal experience. In our study, Bayesian network meta-analysis will**

be used to identify differences in efficacy and safety between diverse traditional Chinese drugs for oral squamous cell carcinoma (OSCC).

Condition being studied: Traditional Chinese medicine, oral squamous cell carcinoma, efficacy and safety.

METHODS

Search strategy: To perform a comprehensive and focused search, experienced systematic review investigators will be invited to develop a search strategy. The plan searched terms are as follows: "oral cancer" or "oral cavity cancer" or "mouth cancer" or "oral cavity carcinomas" or "oral squamous cell carcinoma" or "kou qiang ai" or "kou qiang lin zhuang xi bao ai" or "OC" or "OCC" or "OSCC" and "traditional Chinese medicine" or "traditional Chinese drug" or "Chinese herbal preparation" or "traditional Chinese preparation" or "Chinese materia medica preparation" or Chinese patent medicine" or "zhongyao" or "TCM" or "TCD" et al. The preliminary retrieval strategy for PubMed is provided in Table 1, which will be adjusted in accordance with specific databases.

Participant or population: Patients with histologically proved squamous cell carcinomas of the oral cavity were included in this study. No restrictions regarding age, gender, racial, region, education and economic status. Patients with other malignancies are not included.

Intervention: In the experimental group, OSCC patients must be treated with TCM alone or in combination with other pharmacological interventions. TCM involving extracts from herbs or insects or animals, single or mixture formulas regardless of their compositions or forms. There will be no restrictions with respect to dosage, duration, frequency, or follow-up time of treatment.

Comparator: There will be no restrictions with respect to the type of comparator. The comparators are likely to include placebo, western medical therapies, supportive care, and other therapeutic methods.

Study designs to be included: All available comparative clinical trials that investigated the efficacy and safety of TCM for patients diagnosed with OSCC will be included in this systematic review.

Eligibility criteria: This study will include randomized controlled trials (RCTs) and quasi-RCTs or prospective controlled clinical trials that investigated the efficacy and safety of TCM for patients diagnosed with OSCC. Duplicated studies, papers without sufficient available data, non-comparative clinical trials, case reports and series, meta-analysis, literature reviews, meeting abstracts, and other unrelated studies will be excluded from analysis.

Information sources: Electronic databases including relevant RCTs, quasi-RCTs and high-quality prospective cohort studies were searched from Medline, PubMed, Cochrane Library, Google Scholar, Excerpt Medica Database (Embase), Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (CSJD), Chinese Biomedical Literature Database (CBM) and Wanfang Database will be systematically searched for eligible studies from their inception to September 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will include: i) Overall response rate (ORR) and disease control rate (DCR); ii) Overall survival (OS), the time from the date of randomization to death from any cause.

Additional outcome(s): Secondary outcomes will include: i) Quality of life (QoL) obtained from the corresponding scale. ii) Immune function indicators: CD3+, CD4+, CD8+, NK cells percentage, CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α); iii) Adverse effects: treatment-related toxicity was graded from 0 to IV according to the World Health Organization (WHO) recommendations.

Data management: After screening the literature, the two authors (Dong Wang and XiaoJie Duan) will independently extract the information contained in the eligible literature to form a document feature table. The extracted data are as follows: i) Study characteristics and methodology: country of study, the first author's name, year of publication, randomization, sample size, periods of data collection, follow-up duration, outcome measures, inclusion and exclusion criteria, et al. ii) Participant characteristics: age, gender, tumor stage (staging of the tumor according to the staging system of the International Union Against Cancer-IUAC), tumor size, diagnostic criteria, et al. iii) Interventions: therapeutic means, dose, administration route, course of treatment, and duration of treatment, et al. iv) Outcome and other data: ORR, DCR, OS, QoL, immune indexes [(CD3+, CD4+, CD8+, NK cells percentage, and CD4+/CD8+ cell ratios, and serum cytokines level (IL-2, IL-4, IFN-γ and TNF-α)], and adverse effects, et al. When any data are missing or insufficient, we will contact original authors by using email. If those relevant data are not acquired, we will only analyze the available data, and discuss its impact as a limitation.

Quality assessment / Risk of bias analysis: Two review authors (Dong Wang and XiaoJie Duan) will independently assess the quality of the included RCTs. The assessment tool is provided by Cochrane, which includes seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each item will be evaluated at three levels: low risk, unclear, and high risk. Effective Practice and Organisation of Care (EPOC) guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Yuhui Zhang).

Strategy of data synthesis: First, we will conduct a conventional pairwise meta-analysis of the direct comparison results obtained from the literature. Continuous data will be presented as mean difference (MD) or standardized mean difference (SMD) with their confidence intervals (CIs). Dichotomous data will be recorded as odds ratio (OR) with 95% CIs. Secondly, for the results of indirect comparison, the authors will use ADDIS and R software to conduct network meta-analysis based on random effect model. We will calculate the pooled estimates and 95% CIs of the MD/SMD and OR for primary outcomes. To present indirect comparisons of traditional Chinese medicines, we will make a network diagram. The network graph is mainly composed of nodes and lines. Among them, the node represents a kind of therapy, and the nodes connected by lines indicate that there is a direct or indirect comparative relationship between the two. The node size represents the number of subjects receiving this therapy. The thickness of the line represents the number of studies. Then, we will analyze the outcomes from all direct or indirect comparisons to assess which traditional Chinese drug for OSCC is most effective and estimate the rank probabilities of all the groups based on the Markov chain Monte Carlo method. Heterogeneity of treatment effects across trials was assessed by $\chi 2$ statistics and the I2 statistics. When the P value was >0.1, and I2 was <50%, it suggested that there was no statistical heterogeneity and the Mantel-Haenszel fixed-effects model was used for meta-analysis. Otherwise, a random-effects mode will be used to calculate the outcomes.

Subgroup analysis: When the P value was 50%, we explored sources of heterogeneity with respect to age, tumor stage, region and types of TCM by subgroup analysis and meta-regression.

Sensibility analysis: Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with low-quality. A summary table will report the results of the sensitivity analyses.

Language: Language is limited with English and Chinese.

Country(ies) involved: China.

Other relevant information: i) Publication bias. Funnel plot will be performed to analyze the existence of publication bias if 10 or more studies are included in this meta-analysis. If the funnel chart has poor symmetry, it indicates publication bias. ii) Assess the quality of evidence. The evidence grade will be assessed by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The quality of all evidence will be assessed at four levels: high, moderate, low, and very low.

Keywords: oral squamous cell carcinoma, Bayesian network meta-analysis, traditional Chinese medicine, efficacy.

Dissemination plans: The results of this study will be published in a peer-reviewed journal, and provide reliable evidence for different traditional Chinese drugs on OSCC.

Contributions of each author:
Author 1 - Dong Wang - Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing-original draft.
Author 2 - XiaoJie Duan - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 3 - Yuhui Zhang - Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing-original draft.
Author 4 - Zhen Meng - Funding acquisition, Methodology, Validation, Writing-review & editing.
Author 5 - Jing Wang - Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing-review & editing.