INPLASY PROTOCOL

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Corresponding author:
Lemei Chen

clm0729@126.com

Author Affiliation:
People's Hospital of Weifang Binhai ETDFZ

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

Xiaoaiping injection as adjunct therapy for patients with advanced esophageal carcinoma: A protocol for a systematic review and meta-analysis

Liu, Z[1]; Dong, YL[2]; Zhu, ML[3]; Mu, Y[4]; Chen, LM[5].

Review question / Objective: **Is Xiaoaiping injection (XAPI) effective and safety for patients with advanced esophageal carcinoma (EC)?**
Condition being studied: **Xiaoaiping injection and esophageal carcinoma.**
Information sources: **Electronic databases including Cochrane Library, PubMed, Google Scholar, Web of Science (WOS), Excerpt Medica Database (Embase), Medline, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), China Scientific Journal Database (VIP) and Wanfang Database will be systematically searched for eligible studies from January 2000 to May 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 26 May 2020 and was last updated on 26 May 2020 (registration number INPLASY202050094).

INTRODUCTION

Review question / Objective: **Is Xiaoaiping injection (XAPI) effective and safety for patients with advanced esophageal carcinoma (EC)?**

Rationale: **Xiaoaiping injection (XAPI) has been widely applied as a promising adjunctive drug for esophageal carcinoma (EC). However, the exact effects and safety of XAPI have yet to be systematically investigated. We aimed to summarize the efficacy and safety of XAPI for the treatment of advanced EC through the meta-analysis, in order to provide scientific reference for the design of future clinical trials.**

Condition being studied: Xiaoaiping injection and esophageal carcinoma.

METHODS

Search strategy: To perform a comprehensive and focused search, experienced systematic review researchers will be invited to develop a search strategy. The plan searched terms are as follows: "esophageal cancers" or "esophageal neoplasm" or "esophageal carcinoma" or "esophageal tumor" or "shiguanai" or "shiguanzhongliu" or "EC" and "Xiaoaiping injection" or "XAP injection" or "XAPI" or "Tongguanteng" or "Tongguanteng extract" or "Tongguangteng" or "Tongguangteng extract" or "Marsdenia tenacissima" or "Marsdenia tenacissima extract" or "MTE" et al. An example of search strategy for PubMed database shown in Table 1 will be modified and used for the other databases.

Participant or population: Patients must be cytologically or pathologically confirmed as having EC at a clinically advanced stage. There will be no restrictions regarding age, gender, racial, region, education and economic status. Patients with other malignancies or non-primary EC are not included.

Intervention: In the experimental group, advanced EC patients must be treated with conventional treatment (including chemotherapy, radiotherapy, and targeted therapy) combined with XAPI mediated therapy.

Comparator: In the control group, EC patient treated with the same conventional treatment as intervention group in the same original study.

Study designs to be included: All available RCTs or prospective cohort studies that investigated the efficacy and safety of XAPI-mediated therapy for advanced EC will be included.

Eligibility criteria: This study will include randomized controlled trials (RCTs) or quasi-RCTs, and high-quality prospective cohort studies that compared the efficacy and safety of XAPI with other treatments for patients with advanced EC. Articles without sufficient available data, non-comparative studies, non-peer reviewed articles, meta-analysis, literature reviews, case reports, case series, meeting abstracts, animal studies, letter to the editor, commentaries, editorials, and other unrelated studies will be excluded from analysis.

Information sources: Electronic databases including Cochrane Library, PubMed, Google Scholar, Web of Science (WOS), Excerpt Medica Database (Embase), Medline, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), China Scientific Journal Database (VIP) and Wanfang Database will be systematically searched for eligible studies from January 2000 to May 2020. Language is limited with English and Chinese.

Main outcome(s): The primary outcomes will be the therapeutic effects of treatment according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST Criteria 1.1). a) Overall response rate (ORR); b) Overall survival (OS, which is defined as the time from the date of randomization to death from any cause); c) Disease-free survival (DFS, which is the time from date of random assignment to date of recurrence or death).

Additional outcome(s): Secondary outcomes will include: a) QoL as evaluated by Karnofsky score; b) Immune function; c) Treatment–related adverse effects.

Data management: Two reviewers (Zhen Liu and Yanling Dong) will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention. The following data will be extracted from eligible literatures: a) Study characteristics and methodology: country of study, the first author, year of publication, study design, randomization, periods of data collection, total duration of study, follow-up duration, and withdrawals, et al. b) Participant characteristics: sample size, tumor stage

(staging of the tumor according to the AJCC TNM classification for esophageal cancer), age, gender, ethnicity, pathology diagnosis, pathologic tumor size, inclusion and exclusion criteria, et al. c) Interventions: therapeutic means, manufacturer of the drugs, dosage of XAPI, administration route and cycles, duration of treatment and follow-up time, et al. d) Outcome and other data: ORR, OS, DFS, QoL, immune function and adverse effects, et al. For survival outcomes, Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) will be extracted from trials or be estimated from Kaplan–Meier survival curves by established methods. Dealing with missing data: we will attempt to contact the authors to request the missing or incomplete data. If those relevant data are not acquired, they will be excluded from the analysis. Any disagreements will be resolved by discussion, and a third reviewer (Meili Zhu) will make the final decision. Excluded studies and the reasons for exclusion will be listed in a table.

Quality assessment / Risk of bias analysis: The quality of the included RCTs will be assessed independently by 2 investigators (Zhen Liu and Yanling Dong) in terms of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other bias, according to the guidance of the Cochrane Handbook for Systematic Review of Interventions. Evidence quality will be classified as low risk, high risk, or unclear risk of bias in accordance with the criteria of the risk of bias judgment. The risk of bias judgments across different studies for each of the domains listed will be summarized. EPOC guidelines will be used to assess the risks of non-RCTs. Any disagreements will be resolved via discussion with a third researcher (Meili Zhu).

Strategy of data synthesis: Data from studies judged to be clinically homogeneous will be pooled using Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp., College Station, TX, USA) statistical software. Heterogeneity between studies will be assessed using the Cochran's Q and Higgins I2 statistic. $P < 0.1$ for the Chi2 statistic or an $I2 > 50\%$ will be considered as showing considerable heterogeneity. A fixed effect model will be used to calculate the outcomes when statistical heterogeneity is absent; otherwise, the random effects model was considered according to the DerSimonian and Laird method. The Mantel–Haenszel method will be applied for pooling of dichotomous data and results will be presented as relative risk (RR) with their 95% confidence intervals (CIs). Inverse variance method will be used for pooling of continuous data and results will be presented as standardized mean difference (SMD) with their 95% CIs. A two-tailed P value < 0.05 was considered statistically significant.

Subgroup analysis: If the data are available and sufficient, subgroup and meta-regression analysis will be conducted to explore the source of heterogeneity with respect to age, gender, tumor stage, region, course of treatment and therapeutic regimens.

Sensibility analysis: Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with high bias risk. 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: Publication bias analysis We will detect publication biases and poor methodological quality of small studies using funnel plots if 10 or more studies are included in the meta-analysis. Begg's and Egger regression test will be utilized to detect the funnel plot asymmetry. If reporting bias is suspected, we will consult the study author to get

more information. If publication bias existed, a trim-and-fill method should be applied to coordinate the estimates from unpublished studies, and the adjusted results were compared with the original pooled RR. Evidence evaluation The evidence grade will be determined by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). The quality of all evidence will be evaluated as 4 levels (high, moderate, low, and very low).

Keywords: Xiaoaiping injection, esophageal carcinoma, efficacy, meta–analysis, safety.

Dissemination plans: We will disseminate the results of this systematic review by publishing the manuscript in a peer-reviewed journal or presenting the findings at a relevant conference.

Contributions of each author:

Author 1 - Zhen Liu - Conceptualization; Investigation; Methodology; Project administration; Supervision; Writing-original draft; Writing-review & editing.
Author 2 - Yanling Dong - Investigation; Methodology; Writing-original draft.
Author 3 - Meili Zhu - Investigation; Methodology; Writing-original draft.
Author 4 - Ying Mu - Methodology; Funding acquisition; Writing-review & editing.
Author 5 - Lemei Chen - Conceptualization; Methodology; Project administration; Supervision; Writing-review & editing.