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Immunotherapy vs platinum for advanced or metastatic thymic carcinoma
A protocol for systematic review and meta analysis

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Abstract
Background: Thymic carcinoma is a rare malignancy, and platinum-based chemotherapy has not previously been established as a standard treatment for advanced or metastatic thymic carcinoma. With the breakthrough and progress of immunotherapy, the possibility of curing thymic carcinoma has greatly increased. Some clinical trials have reported that compared with traditional platinum-based chemotherapy, the use of programmed death 1 and programmed death ligand 1 inhibitors alone can benefit patients and effectively prolong their overall survival. We compare the efficacy of single immunotherapy with traditional platinum-based chemotherapy in a systematic review and meta-analysis to provide a reliable basis for clinicians.

Methods: Pubmed (Medline), Web of Science, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar will be searched for relevant randomised controlled trials, quasi- randomised controlled trials, and Hi-Q(high quality) prospective cohort trials published or unpublished in any language before March 1, 2021. Subgroup analysis will be performed in tumor pathological stage and ethnicity. INPLASY registration number: INPLASY2020110060.

Results: The results of this study will be published in a peer-reviewed journal.

Conclusion: The results of this systematic review and meta-analysis will provide a basis for clinicians to formulate the best chemotherapy regimen for patients, as well as a research clue for clinical researchers in this field. The results of this study will expand the treatment options for thymic carcinoma, but due to the nature of the disease and intervention, large sample clinical trials are not abundant, so we will include some high-quality small sample trials, which may cause high heterogeneity.

INPLASY registration number: INPLASY2020110060

Abbreviations: CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, MeSH = Medical Subject Heading, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols, RCTs = randomized controlled trials, RR = relative risk, SMD = standardized mean difference.

Keywords: immunotherapy, platinum-based chemotherapy, thymic carcinoma

1. Introduction

Thymic cancer is a rare malignant disease with an incidence rate of approximately 0.02 per 100,000 person-years[1,2]. About 30% of patients have advanced to advanced stages at the time of diagnosis. Patients with advanced or metastatic thymic cancer have a poor prognosis. In this case, cytotoxic chemotherapy has been used to prolong patient prognosis[3]. Some retrospective studies and phase 2 clinical trials have been completed to investigate the efficacy of cytotoxic drugs, immune checkpoint inhibitors, and molecular targeted drugs[4–8]. On the basis of these research results, platinum-based chemotherapy has received attention[9,10]. However, standard second-line treatment for advanced or metastatic thymic carcinoma patients previously treated with platinum-based chemotherapy has not yet been established.

Immunotherapy is a relatively new field in the treatment of thymic carcinoma. Some clinical trials reported that PD-1 and PD-L1 inhibitors alone have better application prospects than platinum-based chemotherapy[11–15]. We will conducted a systematic review and meta analysis on the efficacy comparison between immunotherapy and traditional platinum-based chemotherapy, so as to provide a reliable basis for further promotion of

immunotherapy and for clinicians to formulate the best chemotherapy regimen for patients with advanced or metastatic thymic carcinoma.

2. Objective

We will evaluate the efficacy of platinum based chemotherapy and immunotherapy with or without radiotherapy for patients with advanced or metastatic thymic carcinoma.

3. Methods

This protocol is conducted according to the preferred reporting items for systematic review and meta-analysis protocols statement[16]. We will report the results of this systematic review and meta-analysis adhere to the preferred reporting items for systematic reviews and meta-analyse guidelines[17]. This protocol has been registered in the INPLASY network (registration number: INPLASY2020110060).

3.0. Patient and public involvement: This study will be based on published or unpublished studies and records and will not involve patients or the public directly.

3.1. Eligibility criteria
3.1.1. Types of studies. Randomised controlled trials and quasi- randomised controlled trials published or unpublished will be included, which have been completed and compared postoperative platinum-base chemotherapy versus immunotherapy for patients with advanced or metastatic thymic carcinoma.

3.1.2. Types of participants. The participants will be adults diagnosed with advanced or metastatic thymic carcinoma histologically or cytologically confirmed who were treated with platinum-based chemotherapy, or immunotherapy. No restrictions on ethnicity, sex, education, and economic status will be applied.

3.1.3. Types of interventions. According to the means of postoperative chemotherapy for patients with advanced or metastatic thymic carcinoma, the trials included will be divided into the following categories.

- Immunotherapy versus molecular targeted therapy
- Immunotherapy versus anti-angiogenic agents
- Postoperative platinum-base chemotherapy versus molecular targeted therapy
- Platinum-based chemotherapy versus anti-angiogenic agents
- Platinum-based chemotherapy versus immunotherapy

3.1.4. Types of outcome measures
3.1.4.1. Primary outcomes. The primary outcomes will be postoperative overall survival of patients with advanced or metastatic thymic carcinoma who were treated with chemotherapy.

3.1.4.2. Secondary outcomes. We will assess the 5-year survival, median survival, recurrence-free survival, quality of life, and adverse events or complications of patients with advanced or metastatic thymic carcinoma who were treated with chemotherapy.

3.2. Information sources

We will search Pubmed (Medline), Embase, Google Scholar, Cancerlit, and the Cochrane Central Register of Controlled Trials for related studies published before March 1, 2021 without language restrictions.

3.3. Search strategy

We will use the relevant keywords or subject terms adhered to medical subject heading terms to search for eligible studies in the electronic databases which were mentioned above without language restrictions. The Pubmed search strategies are shown in Table 1.

3.4. Data collection and analysis

We will utilize the measures described in the Cochrane Handbook for Systematic Reviews of Interventions to pool the evidence[18].

3.4.1. Study selection. Two reviewers (JKQ, ZWT) will investigate each title and abstract of all literatures searched independently and identify whether the trials meet the inclusion criteria as designed and described in this protocol. Two authors (JKQ, ZWT) will in duplicate and independently screen the full text of all potential eligible studies to exclude irrelevant studies or determine eligibility. The 2 reviewers will list all the studies included and document the primary reasons of exclusion for studies that do not conform to the inclusion criteria. Disagreements between the 2 authors will be resolved by discussing with the third author (YNZ), if necessary, consulting with the fourth author (CC). We will show the selection process in details in the preferred reporting items for systematic review and meta-analysis protocols flow chart.

3.4.2. Data extraction and management. The 2 authors (JKQ, ZWT) will extract the following data independently from the studies included.

- Study characteristics and methodology: publication date, the first author, country, randomization, study design, periods of data collection, follow-up duration, total duration of study, and withdrawals, etc.

Table 1

Pubmed search strategies.

Query	Search term
# 1	Thymomas or carcinoma, thymic or carcinomas, thymic or thymic carcinoma or thymic carcinomas
# 2	Platinum-based chemotherapy or chemotherapy or chemotherapies or docetaxel or taxotere or docetaxel or pemetrexed or alimta or pemetrexed or cisplatin or carboplatin
# 3	Immunotherapy or immunotherapies or immunosuppression or PD1 inhibitors or PDL1 inhibitors
# 4	Randomized controlled trial or controlled clinical trial or randomized or placebo or drug therapy or randomly or trial or groups not animals
# 5	# 1 and # 2 and # 3 and # 4

- Participant characteristics: gender, age, tumor stage, pathology diagnosis, ethnicity, performance status, history of smoking, pathologic tumor size, and inclusion criteria, etc.
- Interventions: therapeutic means, drugs, dosage, modality and frequency of administration, etc.
- Outcome and other data: overall survival, 5-year survival, median survival, disease-free survival, 95% confidence intervals, recurrence time, quality of life, adverse events, and complications, etc.

We will record all the date extracted in a pre-designed table and consult the first author of the trial by e-mail before determining eligibility, if the reported data of which are unclear or missing.

3.5. Assessment of risk of bias in included studies

Two authors (JKQ, ZWT) will use the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias of each study included independently based on the following ranges: 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); other bias[19]. Each domain will be assessed as high, low, or uncertain risk of bias. The results and details of assessment will be reported on the risk of bias graph.

3.6. Data analysis

The data will be synthesised by Review Manager 5.3 software. We will conduct a systematic review and meta-analysis only if the data gathered from included trials are judged to be similar enough to ensure a result that is meaningful. The Chi-squared test and I^2 statistic will be used to assess statistical heterogeneity among the trials included in matched pairs comparison for standard meta-analysis. The random effect model will be applied to analyse the data, if there is substantial heterogeneity ($P < .1$ or I^2 statistic $>50\%$) and the trials will be regarded to be obvious heterogeneous. Otherwise, we will utilize fixed effect model to analyse the data. Mantel-Haenszel method will be adopted to pool of the binary data. The results will be reported in the form of relative risk between 95% confidence interval of the date. The continuous data will be pooled by inverse variance analysis method and the results will be shown in the form of standardized mean difference with 95% confidence interval of the date.

3.6.1. Subgroup analysis. If there is high heterogeneity (I^2 statistic $> 50\%$) and the data are sufficient, subgroup analysis will be conducted to search potential causes of heterogeneity. Subgroup analysis will be performed in different methods of postoperative adjuvant therapy, ethnicity, history of smoking, tumor stage, and type of operation.

3.6.2. Sensitivity analysis. Sensitivity analysis will be conducted to assess the reliability and robustness of the aggregation results via eliminating trials with high bias risk.

3.7. Publication bias

If there are 10 or more than 10 trials included, we will construct a funnel plot and use Egger test to assess publication bias. If reporting bias is suspected, we will consult the study author to get more information. If publication bias does exist, we will apply the fill and trim method to analyze publication bias in the trials[20].

3.8. Evidence evaluation

We will evaluate all the evidence according to the criteria of grading of recommendations, assessment, development and evaluation (imprecision, study limitations, publication bias, consistency of effect, and indirectness bias). The quality of all evidence will be evaluated as 4 levels (high, moderate, low, and very low)[20].

4. Discussion

Thymic carcinoma is a highly malignant tumor. Although there are many advanced treatment methods combined with surgical treatment, the prognosis of patients is very poor. Thymectomy is the main treatment for early thymic carcinoma, but the thymic carcinoma that is often detected is already advanced. Adjuvant therapy plays a key role, which is a key factor that contributes to the overall survival of patients. Thymic carcinoma mainly occurs in middle-aged and elderly patients, whose quality of life and physical fitness are poor. Therefore, what we need to pursue now is therapies that can significantly improve overall survival rates with fewer side effects. Immunotherapy is a new field in the treatment of advanced or metastatic thymic carcinoma. Many trials have reported that PD-1 and PD-L1 inhibitors can benefit patients more than traditional platinum-based chemotherapy. We will conduct a systematic, comprehensive and objective assessment of immunotherapy and platinum-based adjuvant chemotherapy. The results of this study will provide the basis for clinicians to formulate the best postoperative adjuvant treatment strategies for patients with advanced or metastatic thymic carcinoma, and provide scientific clues for researchers in this field.

Author contributions

Chun Chen is the guarantor of the article. And Jiekun Qian and Zhangwei Tong conceived and designed the study. Jiekun Qian and Zhangwei Tong drafted this protocol. Jiekun Qian and Zhangwei Tong and Yannan Zhang will perform the search, screening and extraction. Chun Chen have strictly reviewed this protocol and approved of publication. Jiekun Qian and Zhangwei Tong contributed equally to this work.

Author contributions

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Validation: Jiekun Qian, Chun Chen.
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