INPLASY PROTOCOL

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Corresponding author:
Weixian Jiang

jwxmed@163.com

Author Affiliation:
Affiliated Hangzhou Chest Hospital, Zhejiang University School of Medicine.

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None declared.

Efficacy and safety of immunotherapy in the treatment of malignant pleural mesothelioma: A protocol of meta-analysis

Shen, Y[1]; Yu, G[2]; Ye, B[3]; Xu, K[4]; Jiang, W[5].

Review question / Objective: **There is still a lack of evidence-based medicine evidence to assess the safety and efficacy of immunotherapy for MPM. With this aim, we designed this meta-analysis based on randomized controlled trials (RCTs) to further evaluate the safety and efficacy of immunotherapy in the treatment of MPM.**

Condition being studied: **Malignant pleural mesothelioma (MPM) is a rare malignant tumor of pleural mesothelial origin, which accounts for only about 0.3% of all malignant tumors. MPM is extremely aggressive, difficult to cure, and has a very poor prognosis. Exposure to asbestos is an important cause of MPM development. For patients with early MPM, surgical treatment is feasible if appropriate after preoperative evaluation. However, for the majority of patients with MPM, they are diagnosed at an intermediate to advanced stage and lose the opportunity for surgery. Pemetrexed in combination with platinum-based chemotherapy is the first-line treatment of choice for advanced, unresectable MPM. However, from a comprehensive assessment, the survival benefit of this regimen for MPM is limited, with 5-year survival rates still below 10%, so more effective treatments are urgently needed.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 September 2021 and was last updated on 17 September 2021 (registration number INPLASY202190054).

INTRODUCTION

Review question / Objective: **There is still a lack of evidence-based medicine evidence to assess the safety and efficacy of immunotherapy for MPM. With this aim, we designed this meta-analysis based on randomized controlled trials (RCTs) to further evaluate the safety and efficacy of immunotherapy in the treatment of MPM.**

Rationale: **Immunotherapy is a new hope for the treatment of malignant tumors in recent years, and has shown very good**

results in thoracic tumors such as lung cancer. Immunotherapy also plays an important role in the treatment of MPM. However, the effectiveness and safety of immunotherapy in the treatment of MPM is still controversial.

Condition being studied: Malignant pleural mesothelioma (MPM) is a rare malignant tumor of pleural mesothelial origin, which accounts for only about 0.3% of all malignant tumors. MPM is extremely aggressive, difficult to cure, and has a very poor prognosis. Exposure to asbestos is an important cause of MPM development. For patients with early MPM, surgical treatment is feasible if appropriate after preoperative evaluation. However, for the majority of patients with MPM, they are diagnosed at an intermediate to advanced stage and lose the opportunity for surgery. Pemetrexed in combination with platinum-based chemotherapy is the first-line treatment of choice for advanced, unresectable MPM. However, from a comprehensive assessment, the survival benefit of this regimen for MPM is limited, with 5-year survival rates still below 10%, so more effective treatments are urgently needed.

METHODS

Participant or population: Pathologically confirmed MPMs will be participants in this study. The demographic factors such as ethnicity, gender, and age of the participants will be no restrictions.

Intervention: Immunotherapy (including all currently known immune checkpoint inhibitors [ICIs]) as monotherapy or immunotherapy in combination with other therapies for the treatment of MPM.

Comparator: Other regimens used for MPM treatment (excluding immunotherapy), and placebo will be also applicable.

Study designs to be included: The studies included in this protocol are completed RCTs, both published and unpublished, that have evaluated the efficacy and safety of using immunotherapy for the treatment of MPM.

Eligibility criteria: The studies included in this protocol are completed RCTs, both published and unpublished, that have evaluated the efficacy and safety of using immunotherapy for the treatment of MPM. We will exclude case reports, retrospective studies, quasi-RCTs, prospective cohort studies, reviews, and studies published in languages other than Chinese and English.

Information sources: We will search for studies that match the study topic in March 2022 through Embase, Scopus, Pubmed, Web of Science, Cochrane Library, Wanfang Database, and China National Knowledge Infrastructure (CNKI). We will review the reviews in the field to identify other studies that may meet the criteria. In the meantime, we will search the official European Society for Medical Oncology, American Society of Clinical Oncology, and Chinese Society of Clinical Oncology website for unpublished clinical trials on immunotherapy for MPM.

Main outcome(s): The outcomes included the objective response rate (ORR), disease control rate (DCR), mPFS, mOS, and adverse events (AEs). Studies reporting at least one outcome indicator will be included.

Data management: Study selection - Study selection will be conducted independently by two investigators. The articles obtained during the search phase will be imported into Endnote X9.2 for management. Duplicate articles obtained through Endnote screening will be removed first. Further investigation by title, abstract and full text to exclude articles that do not meet the inclusion criteria, and finally the eligible articles will be left. The references of the review will also be further screened to include additional eligible articles. Results from two investigators will be cross-checked and inconsistent results will be decided through discussion with a third investigator. Data extraction - The same two investigators as in the study selection phase of the study will perform data

extraction independently from the articles that meet the criteria. As in the study selection phase, the results obtained will be cross-checked and any discrepancies will also be discussed with the third investigator. The following data will be extracted from the included articles: name of the first author, publication year, countries, type of study, name of clinical trial, number of registration, phase of study, sample size, male ratio, age, main inclusion criteria, intervention model, randomization method, masking, histological types of MPM, the name of ICI drug, dose of ICIs, ICI treatment modality (single agent or combination), target of ICIs, programmed death ligand-1 receptors [PD-L1] expression level, control group treatment regimen and dose, number of treatment lines, ORR, DCR, mPFS, mOS, and AEs.

Quality assessment / Risk of bias analysis: The same two investigators will independently assess the risk of bias of each included article. We will use the Cochrane Handbook for Systematic Reviews of Interventions to evaluate the risk of bias. We will evaluate the risk of bias of the article based on selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. High, low or uncertain risk of bias will be reported for each domain. The results and details of assessment will be demonstrated though the risk of bias graph.

Strategy of data synthesis: We will perform the relevant statistical analysis using Review Manager 5.3 (Revman) software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). If only Kaplan-Meier curves but not specific mPFS and mOS are reported in the article, we will extract the survival data from the Kaplan-Meier curves using the Engauge Digitizer 4.1 software. The pooled HRs for PFS and OS, risk ratios (RRs) for ORRs and DCRs, and odds ratios (ORs) for different AEs with 95% confidence intervals (CIs) will be calculated using Revman. Q-statistic will be used to evaluate the statistical heterogeneity between studies. A Q-statistic $P < 0.1$ or an $I2 > 50\%$ will be considered to have significant heterogeneity between studies. When there is significant heterogeneity, a random-effects model will be used for analysis, while when heterogeneity is not significant, a fixed effects model will be used. $P < 0.05$ will be considered to have statistical significance. HR > 1 will indicate a greater rate of progression or death with ICIs treatment, RR > 1 will indicate a greater overall response, and OR > 1 will indicate greater toxicity of ICIs.

Subgroup analysis: When heterogeneity is apparent, subgroup analysis will be performed on predetermined parameters (such as age, sex, phase of study, histological types of MPM, the name of ICI drug, ICI treatment modality (single agent or combination), target of ICI, PD-L1 expression level, control group treatment regimen, number of treatment lines) to explore the sources of heterogeneity. when the extracted data are sufficient.

Sensitivity analysis: A sensitivity analysis will be performed by reporting the results with and without a certain article to evaluate the reliability and robustness of the analysis results.

Language: No restriction.

Country(ies) involved: China.

Other relevant information: Publication bias - Funnel plots and Egger test will be used to assess publication bias when > 10 eligible articles are included. If publication bias does exist, the fill and trim method will be used to further analyze the publication bias in the studies. Evidence evaluation - The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline will be used to evaluate the strength of the body of evidence. Evidence quality of high, moderate, low, or very low will be reported for complete research report.

Keywords: malignant pleural mesothelioma, immunotherapy, efficacy, safety, meta-analysis.

Contributions of each author:
Author 1 - Yanqin Shen.
Email: yanqinshen@yeah.net
Author 2 - Guocan Yu.
Email: dabaitwo@163.com
Author 3 - Bo Ye.
Email: yeboboye@126.com
Author 4 - Kan Xu.
Email: xukanmed@163.com
Author 5 - Weixian Jiang.
Email: jwxmed@163.com