INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Precise medicine of PD1/PD-L1 inhibitor immunotherapy combined radiotherapy for inoperable advanced lung cancer A protocol for systematic review and meta-analysis

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Review question / Objective: **This study aims to evaluate the efficacy and safety of PD1/PD-L1 inhibitor immunotherapy combined chemotherapy for inoperable advanced lung cancer.**
Condition being studied: **PD-1/PD-L1 inhibitors are a group of immune checkpoint inhibitors immunotherapy for cancer treatment. These immune checkpoint inhibitors are becoming first-line treatments for several types of cancer. Radiotherapy for cancer is a traditional treatment and the therapeutic effect is not satisfactory due to the side effect of chemotherapeutic drugs.**
Information sources: **We will utilize PubMed, PubMed Central, EMbase, Medline, CNKI, WAN FANG Database, and Web of Science to screen eligible studies published from January 1st, 2015 to December 30th, 2020. Two reviewers will extract data and evaluate the risk of bias independently. The quality of the included studies will be evaluated using the RevMan 5.3 software for data analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2021 and was last updated on 24 April 2021 (registration number INPLASY202140123).

INTRODUCTION

Review question / Objective: **This study aims to evaluate the efficacy and safety of PD1/PD-L1 inhibitor immunotherapy combined chemotherapy for inoperable advanced lung cancer.**

Rationale: **Lung cancer is the most common tumor in the world, and its morbidity and mortality rank first among all kinds of malignant tumors. According to statistics, the number of new cases of lung cancer accounts for 12.9% of all tumor**

types every year. Lung cancer is a malignant disease occurring in the bronchial mucosa epithelium. And 85% were non-small cell lung cancer (NSCLC). With the deepening of clinical studies on the immune escape mechanism of the tumor, it is found that Programmed Cell Death 1 (PD-1)/Programmed Cell Death ligand 1 (PD-1 ligand, PD-L1) can suppress the immune response through immune escape, immunosuppression, and clearance and other mechanisms to enhance the tumor microenvironment on the body's normal immunity resistance effect. Regarding Immunosuppressive agents targeting the PD-1/PD-L1 pathway, its efficacy and safety have been confirmed 5, in large clinical trials of locally advanced maintenance chemotherapy and advanced first-line and second-line treatments in NSCLC6, but the domestic clinical reports of anti-PD-1 /PD-L1 single treatment combined radiotherapy for inoperable advanced NSCLC are seldom reviewed.

Condition being studied: PD-1/PD-L1 inhibitors are a group of immune checkpoint inhibitors immunotherapy for cancer treatment. These immune checkpoint inhibitors are becoming first-line treatments for several types of cancer. Radiotherapy for cancer is a traditional treatment and the therapeutic effect is not satisfactory due to the side effect of chemotherapeutic drugs.

METHODS

Search strategy: We will utilize PubMed, PubMed Central, EMbase, Medline, CNKI, WAN FANG Database, and Web of Science to screen eligible studies published from January 1st, 2015 to December 30th, 2020. Two reviewers will extract data and evaluate the risk of bias independently. The quality of the included studies will be evaluated using the RevMan 5.3 software for data analysis.

Participant or population: Participants conformed to Guidelines for diagnosis and treatment of inoperable advanced lung cancer will be included, regardless of gender, age, and race.

Intervention: The control group was treated with radiotherapy alone, and the treatment group was treated with PD1/PD-L1 inhibitor combined radiotherapy, regardless of the dosages.

Comparator: Data will be extracted by 2 reviewers independently (Xiaolan Lv and Yanling Ding). Any disagreement will be resolved through discussion until consensus is reached or by a third author. The following data will be extracted: General information: author, year of publication, the country of the study conducted; database .Participant characteristics, including age, gender, stage of lung cancer, therapeutic method; total number of patients included in the study; Intervention details: doses of radiotherapy, dose of anti-PD-1 /PD-L1 and the time of application. Adverse effect and Quality assessment tools.

Study designs to be included: Randomized controlled trials involving PD1/PD-L1 inhibitor combined radiotherapy for inoperable advanced lung cancer will be included. The language will be limited to Chinese and English.

Eligibility criteria: Any disagreement will be resolved through discussion until consensus is reached or by a third author. The following data will be extracted: General information: author, year of publication, the country of the study conducted; database. Participant characteristics, including age, gender, stage of lung cancer, therapeutic method; total number of patients included in the study; Intervention details: doses of radiotherapy ,dose of anti-PD-1 /PD-L1 and the time of application. Adverse effect and Quality assessment tools

Information sources: We will utilize PubMed, PubMed Central, EMbase, Medline, CNKI, WAN FANG Database, and Web of Science to screen eligible studies published from January 1st, 2015 to December 30th, 2020. Two reviewers will extract data and evaluate the risk of bias independently. The quality of the included

studies will be evaluated using the RevMan 5.3 software for data analysis.

Main outcome(s): The main outcome indicator was the clinical efficiency, and the efficacy was evaluated according to overall response rate (ORR) and disease control rate (DCR) for immune checkpoint inhibitors, progression-free survival rates (PFS) for lung cancer, and a significant improvement in PFS was observed in lung cancer.

Additional outcome(s): Additional outcomes included white blood cell count and incidence of adverse events, with a combined hazard ratio and 95% confidence interval.

Data management: Data will be extracted by 2 reviewers independently (Xiaolan Lv and Yanling Ding). Any disagreement will be resolved through discussion until consensus is reached or by a third author. The following data will be extracted: General information: author, year of publication, the country of the study conducted; database. Participant characteristics, including age, gender, stage of lung cancer, therapeutic method; total number of patients included in the study; Intervention details: doses of radiotherapy ,dose of anti-PD-1 /PD-L1 and the time of application. Adverse effect and Quality assessment tools.

Quality assessment / Risk of bias analysis: The characteristic included random sequence generation, participant blinding, outcome assessor blinding, and other generic sources of bias, attrition, and exclusions. The methodological quality of randomized controlled trials will be assessed by Cochrane risk of bias.

Strategy of data synthesis: The analysis and synthesis of data will be conducted by RevMan 5.3 software. Risk ratio with a 95% confidence interval (CI) will be used to determine dichotomous data or standardized mean differences (95%) CI will be used to analyze the continuous data.

Subgroup analysis: To seek whether there is a possible causes of heterogeneity, we will perform subgroup analysis if there are a sufficient number of literatures.

Sensitivity analysis: In order to make sure the results are reliable, we will perform sensitivity analysis to eliminate the impact of low-quality literatures after validation of inputted data and subgroup analysis. But, if all included literatures are at high risk of bias, we will not perform sensitivity analysis.

Language: English.

Country(ies) involved: China.

Keywords: Precise medicine, PD1/PD-L1 inhibitor, radiotherapy, lung cancer, immunotherapy, systematic review.

Contributions of each author:
Author 1 - Gang Liu.
Author 2 - Xiaolan Lv.
Author 3 - Yanling Ding.
Author 4 - Yongbo Guo.