INPLASY PROTOCOL

To cite: Kang et al. The efficacy and safety of immune-checkpoint inhibitor plus chemotherapy versus chemotherapy for non-small cell lung cancer: an updated systematic review and meta-analysis. Inplasy protocol 202250156. doi: 10.37766/inplasy2022.5.0156

Received: 28 May 2022

Published: 28 May 2022

Corresponding author:
Mingxian Li

mingxian@jlu.edu.cn

Author Affiliation:
Department of Respiratory, The First Hospital of Jilin University , Changchun, China.

Support: **81670080 and 20210101237JC.**

Review Stage at time of this submission: **Completed but not published.**

Conflicts of interest:
None declared.

The efficacy and safety of immune-checkpoint inhibitor plus chemotherapy versus chemotherapy for non-small cell lung cancer: an updated systematic review and meta-analysis

Kang, J[1]; Zhang, X[2]; Tian, X[3]; Xu, Y[4]; Li, J[5]; Li, M[6].

Review question / Objective: **Population: histologically confirmed advanced NSCLC patients; Intervention: received immune-checkpoint inhibitor plus chemotherapy; Comparison:received chemotherapy; Outcome: reported OS, PFS, ORR and TRAEs; Study design: RCT.**
Condition being studied: **Lung cancer is the primary cause of cancer-related deaths, with an estimated 2.20 million new cases and 1.79 million deaths every year, and 85% of all primary lung cancers are non-small cell lung cancer.**
Eligibility criteria: **Studies were considered eligible if they met the following criteria: (1) being an randomized controlled trial published in English, (2) histologically confirmed advanced NSCLC patients, (3) reported OS, PFS, ORR and TRAEs, (4) the intervention group received immune-checkpoint inhibitor plus chemotherapy, while the control group received chemotherapy, (5) When numerous papers reporting the same trial were found, the most current or most complete publications were chosen. The following were the exclusion criteria: (1) duplicate articles, (2) reviews, meta-analyses, case reports, editorials and letters, (3) molecular biology or animal research, (4) retrospective or prospective observational cohort studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2022 and was last updated on 28 May 2022 (registration number INPLASY202250156).

INTRODUCTION

Review question / Objective: **Population: histologically confirmed advanced NSCLC patients; Intervention: received immune-checkpoint inhibitor plus chemotherapy; Comparison:received chemotherapy; Outcome: reported OS, PFS, ORR and TRAEs; Study design: RCT.**

Rationale: **Immune-checkpoint inhibitors(ICIs) plus chemotherapy show**

potential therapeutic effects in non-small cell lung cancer(NSCLC). Whereas, it is uncertain if the combined treatment is preferable to chemotherapy.

Condition being studied: Lung cancer is the primary cause of cancer-related deaths, with an estimated 2.20 million new cases and 1.79 million deaths every year, and 85% of all primary lung cancers are non-small cell lung cancer.

METHODS

Search strategy: Two independent reviewers (Jing Kang and Jun Zhang) conducted a systematic search of PubMed, EMBASE databases, Cochrane Library for relevant articles published before February 2022. We used the following text words as search terms: "carcinoma, non-small-cell lung" AND "immune therapy" OR "immune checkpoint blockade" OR "immune checkpoint inhibitor" OR "PD-1" OR "PD-L1" OR "CTLA-4" OR "durvalumab" OR "avelumab" OR "tremelimumab" OR "atezolizumab" OR "nivolumab" OR "pembrolizumab" OR "ipilimumab" OR "immune vaccine" AND "randomized controlled trial".

Participant or population: Histologically confirmed advanced non-small cell lung cancer patients.

Intervention: Received immune-checkpoint inhibitor plus chemotherapy.

Comparator: Received chemotherapy.

Study designs to be included: RCT.

Eligibility criteria: Studies were considered eligible if they met the following criteria: (1) being an randomized controlled trial published in English, (2) histologically confirmed advanced NSCLC patients, (3) reported OS, PFS, ORR and TRAEs, (4) the intervention group received immune-checkpoint inhibitor plus chemotherapy, while the control group received chemotherapy, (5) When numerous papers reporting the same trial were found, the most current or most complete publications were chosen. The following were the exclusion criteria: (1) duplicate articles, (2) reviews, meta-analyses, case reports, editorials and letters, (3) molecular biology or animal research, (4) retrospective or prospective observational cohort studies.

Information sources: Two independent reviewers (Jing Kang and Jun Zhang) conducted a systematic search of PubMed, EMBASE databases, Cochrane Library for relevant articles published before February 2022.

Main outcome(s): Our meta-analysis included a total of 12 studies. Overall analysis indicated that ICIs plus chemotherapy could significantly improve OS (HR = 0.79; 95% CI: 0.74–0.84; I2 = 44.4%, P= 0.055), PFS (HR = 0.62; 95% CI: 0.59–0.67; I2 =75.3%, P = 0.000), and ORR (RR = 1.48; 95% CI: 1.27–1.73; I2 =79.0%, P = 0.000) when compared to chemotherapy treatments. Subgroup analysis showed that PD-1/PD-L1 inhibitors combined chemotherapy significantly improved OS, PFS and ORR when compared with chemotherapy, with decreased grade 1-2 TRAEs. Besides, female patients with nonsquamous histology might receive more OS and PFS benefit from ICIs plus chemotherapy. Despite the fact that CTLA-4 inhibitors combined chemotherapy increased PFS, there were no benefits in OS and ORR. When PD-L1/CTLA-4 inhibitors were added to chemotherapy, the risk of grade 3-5 adverse events increased, whereas PD-1inhibitors did not.

Quality assessment / Risk of bias analysis: The Cochrane Risk of Bias tool was used to assess the risk of bias in the included studies. The data extraction and the risk of bias were conducted independently by two reviewers (Jing Kang and Jun Zhang).

Strategy of data synthesis: We estimated the pooled HR and 95% CI for OS and PFS, as well as the pooled OR and 95% CI for ORR and TRAEs. To investigate heterogeneity, I2 statistics were calculated. If the I2 value is more than 50%, a random-effect model was used to pool the results;

otherwise, a fixed-effect model was utilized. Begg's and Egger's tests were used to assess the risk of publication bias across studies, with a P value of <0.05 indicating the existence of bias. To test the stability of the results, sensitivity analyses were performed. Stata version 12 was used for all statistical analyses.

Subgroup analysis: Subgroup analysis revealed that PD-L1 inhibitors combined with chemotherapy, PD-1 inhibitors combined with chemotherapy, were associated with improved OS(HR =0.82; 95% CI: 0.75–0.91; I2= 0.0%; P =0.685; HR = 0.68; 95% CI: 0.60–0.76; I2= 34.1%, P =0.194, respectively) ; PFS (HR = 0.62; 95% CI: 0.56–0.68; I2= 58.3%, P =0.066; HR = 0.53; 95% CI: 0.48–0.59; I2= 39.3%, P =0.143, respectively), and ORR (RR = 1.36; 95% CI: 1.19–1.56, I2= 13.3%, P =0.326; RR = 1.66; 95% CI: 1.35–2.04; I2= 75.5%, P =0.001, respectively). However, CTLA-4 inhibitors combined with chemotherapy only improved PFS (HR = 0.85; 95% CI: 0.74–0.97, I2= 0.0%, P =0.359), but didn't improve OS (HR = 0.90; 95% CI: 0.78–1.05; I2= 0.0 %, P =0.834) and ORR(RR = 0.99; 95% CI: 0.85–1.15; I2= 74.8%, P =0.046).

Sensitivity analysis: Because there was significant heterogeneity in PFS, ORR, and TRAEs, we assessed the influence of each study on the pooled results. The results revealed that the outcomes of OS, PFS , ORR , grade 1-2 TRAEs),and grade 3-5 TRAEs were reliable and stable.

Language: Being an randomized controlled trial published in English.

Country(ies) involved: China.

Keywords: Immune checkpoint inhibitor; chemotherapy; combination; non–small cell lung cancer; efficacy and safety.

Contributions of each author:
Author 1 - Jing Kang.
Author 2 - Jun Zhang.
Author 3 - Zongsheng Tian.
Author 4 - Ye Xu.
Author 5 - Jiangbi Li.
Author 6 - Mingxina Li.