INPLASY PROTOCOL

To cite: Kang et al. Heterogeneity between subgroups of chemoimmunotherapy as first-line treatment for extensive-stage small cell lung cancer: a Meta-analysis and systematic review. Inplasy protocol 202330064. doi: 10.37766/inplasy2023.3.0064

Received: 17 March 2023

Published: 17 March 2023

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Support: **None.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Heterogeneity between subgroups of chemoimmunotherapy as first-line treatment for extensive-stage small cell lung cancer: a Meta-analysis and systematic review

Kang, WW[1]; Han, HD[2]; Song, Y[3].

Review question / Objective: **Currently, the treatment of lung cancer is an era of precision therapy, and chemoimmunotherapy is a better first-line treatment for ES-SCLC patients. At this stage, our main goal is to select effective and reliable survival predictors and screen out suitable target populations for first-line chemoimmunotherapy, so as to maximize the therapeutic efficacy of ES-SCLC. The purpose of this meta-analysis was, by comparing OS-HR / PFS-HR of first-line chemoimmunotherapy of ES-SCLC patients in each clinical characteristics subgroup, to select the dominant groups more suitable for this regimen and the advantages of different chemoimmunotherapies. And whether appropriate clinical features can predict the survival benefit of ES-SCLC patients, so as to better guide clinical treatment.Screening out the population suitable for first-line chemoimmunotherapy can improve the therapeutic effect of ES-SCLC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 March 2023 and was last updated on 17 March 2023 (registration number INPLASY202330064).

INTRODUCTION

Review question / Objective: **Currently, the treatment of lung cancer is an era of precision therapy, and chemoimmunotherapy is a better first-line treatment for ES-SCLC patients. At this stage, our main goal is to select effective and reliable survival predictors and screen out suitable target populations for first-line chemoimmunotherapy, so as to maximize the therapeutic efficacy of ES-SCLC. The purpose of this meta-analysis was, by comparing OS-HR / PFS-HR of first-line chemoimmunotherapy of ES-SCLC patients in each clinical characteristics subgroup, to**

select the dominant groups more suitable for this regimen and the advantages of different chemoimmunotherapies. And whether appropriate clinical features can predict the survival benefit of ES-SCLC patients, so as to better guide clinical treatment.Screening out the population suitable for first-line chemoimmunotherapy can improve the therapeutic effect of ES-SCLC.

Condition being studied: Lung cancer is one of the most common malignancies in the world, and small cell lung cancer accounts for 15%-20% of the total incidence of lung cancer. SCLC is a kind of aggressive neuroendocrine tumor derived from bronchial epithelial cells, which is characterized by rapid progression, high degree of malignancy, easy recurrence, and poor prognosis. According to the two-stage staging method of the American Legionnaires Lung Cancer Society, SCLC is generally divided into limited-stage and extensive-stage. In addition, about 60%-70% of SCLC patients have distant metastasis at the time of diagnosis. In the past 30 years, the clinical treatment strategies of ES-SCLC were mainly chemotherapy and radiotherapy, but the effective time of these treatments was short and local recurrence or distant metastasis will occur soon. Overall, the 5-year survival rate of ES-SCLC patients is less than 2%. Therefore, we urgently need new treatments for this recalcitrant cancer. In recent years, immunotherapy has shown good anti-tumor activity in lung cancer, among which immune checkpoint inhibitors have become the focus of research. Tumor cells suppress the immune system through immune checkpoint to achieve immune escape. Therefore, blocking immune checkpoint can interrupt the immune escape system of tumor, which can enhance the anti-tumor immunity of human body and improve the survival rate of tumor patients. However, there are a few studies on the application of immune checkpoint inhibitors alone in the first-line treatment of SCLC, which may be related to the rapid progress of SCLC, the potential immune escape mechanism and the high potential risk of not undergoing chemotherapy. Therefore, we need to combine immunotherapy with other therapies (chemotherapy, radiation, antivascular) to improve efficacy. There is a potential synergistic effect between chemotherapy and immunotherapy. Cytotoxic chemotherapy drugs can induce immunogenic cell death, and then produce molecular signals that promote the uptake of cancer cell death fragments by antigen-presenting cells, thus enhancing anti-tumor activity in coordination with immune checkpoint inhibitors. Currently, immunotherapy plus chemotherapy is a better first-line treatment option for ES-SCLC patients, and has accumulated a number of phase II and III clinical research data. Screening out the population suitable for first-line chemoimmunotherapy can improve the therapeutic effect of ES-SCLC. Therefore, the purpose of this meta-analysis was, by comparing OS-HR / PFS-HR of first-line chemoimmunotherapy of ES-SCLC patients in each subgroup, to select the dominant groups more suitable for this regimen and the advantages of different chemoimmunotherapies. And whether appropriate clinical features can predict the survival benefit of ES-SCLC patients, so as to better guide clinical treatment.

METHODS

Search strategy: Two authors independently searched the database. The search terms were " extensive-small cell lung cancer ", " Chemoimmunotherapy ", " PD-1 Inhibitors ", " Pembrolizumab ", " Nivolumab ", " Serplulimab ", " Cemiplimab ", " PD-L1 Inhibitors ", " Atezolizumab ", " Durvalumab ", " Adebrelimab ", " Avelumab ", " CTLA-4 Inhibitors ", " Ipilimumab ", " Tremelimumab ", " Randomized Controlled Trial ". PubMed, EMBASE, and Cochrane Library databases were searched from inception to December 3, 2022. We also reviewed the main conferences from January 1, 2020 to December 3, 2022, including the conference literature of the American Society of Clinical Oncology (ASCO), the World Conference on Lung

Cancer (WCLC) and the European Society of Medical Oncology (ESMO).

Participant or population: Phase II and III randomized controlled trials were conducted in patients with histologically diagnosed unresectable or advanced ES-SCLC who were treated with first-line chemoimmunotherapy or chemotherapy alone.

Intervention: ES-SCLC patients received first-line chemoimmunotherapy, including women or patients with age ≥65 years or patients with positive PD-L1 expression or patients without brain metastases or patients without liver metastases or non-smokers or patients with ECOG PS1 or patients with LDH > ULN or patients receiving cisplatin or non-Asian patients.

Comparator: ES-SCLC patients received first-line chemoimmunotherapy, including men or patients with age < 65 years or patients with negative PD-L1 expression or patients with brain metastases or patients with liver metastases or smokers or patients with ECOG PS0 or patients with LDH≤ULN or patients receiving carboplatin or Asian patients.

Study designs to be included: (1) ES-SCLC stage II or III RCTs; (2) To compare chemoimmunotherapy with chemotherapy as first-line treatment, and immunotherapy mainly includes an immune checkpoint inhibitor; (3) Published in English; (4) The primary outcome measures are OS and/or PFS in the experimental and control groups.

Eligibility criteria: (1) Not ES-SCLC stage II or III RCTs; (2) Comparison of immuno-chemotherapy and chemotherapy as non-first-line treatment, and immunotherapy involves more than one immune checkpoint inhibitor; (3) Not published in English; (4) RCTs with low quality or inconsistent outcome indicators.

Information sources: PubMed, EMBASE, and Cochrane Library databases were searched from inception to December 3, 2022. We also reviewed the main conferences from January 1, 2020 to December 3, 2022, including the conference literature of the American Society of Clinical Oncology (ASCO), the World Conference on Lung Cancer (WCLC) and the European Society of Medical Oncology (ESMO).

Main outcome(s): The primary endpoint was the difference in the efficacy of first-line chemoimmunotherapy in each subgroup, measured by the pooled ratio of OS-HRs or PFS-HRs reported by each subgroup between the experimental group and the control group. We compared the heterogeneity of efficacy to first-line chemoimmunotherapy for ES-SCLC by calculating a specific ratio of hazard ratio. A specific ratio of hazard ratio (eg. HR in female patients to HR in male patients) was calculated for each RCTs and then combined with specific ratio of hazard ratios using the deft method. For example, the ratio of female OS-HR to male OS-HR is less than 1, indicating that the therapeutic effect of women is better. However, this ratio greater than 1 indicates a better therapeutic effect in men.

Quality assessment / Risk of bias analysis: Using the Cochrane bias risk assessment tool , two authors independently assessed the risk of bias of each trial. The study was rated as low (low risk in all fields), high (high risk in one or more fields), and unclear risk of bias (more than 3 fields indicated unclear risk).

Strategy of data synthesis: The primary endpoint was the difference in the efficacy of first-line chemoimmunotherapy in each subgroup, measured by the pooled ratio of OS-HRs or PFS-HRs reported by each subgroup between the experimental group and the control group. For each subgroup, PFS-HR or OS-HR in the experimental group compared with those in the control group, along with their 95% confidence intervals, were derived from each included study. The pooled hazard ratio of OS / PFS was calculated in each subgroup, using a random-effects model. The Q test was used to evaluate the heterogeneity

between studies, and the I2 statistics, which represent the percentage of the total observed variability due to heterogeneity, were also calculated. To avoid the risk of ecological bias in RCTs, a specific ratio of hazard ratio (eg. HR in female patients to HR in male patients) was calculated for each RCTs and then combined with specific ratio of hazard ratios using the deft method. Then, these specific ratio of hazard ratios were combined using a random effects model. For example, the ratio of female OS-HR to male OS-HR is less than 1, indicating that the therapeutic effect of women is better. However, this ratio greater than 1 indicates a better therapeutic effect in men. Sensitivity analysis was performed using a "one study deletion" approach which can determine the sensitivity of the meta-analysis for each results. All tests are two-sided, and the statistical significance depends on a hazard ratio of 95% confidence interval of no greater than 1.00. All statistical analyses were executed using the R (version 4.2.2) and R Studio software. P-values $<$ 0.05 were considered statistically significant.

Subgroup analysis: First, we performed subgroup analysis of first-line chemoimmunotherapy efficacy for clinical characteristics of ES-SCLC patients, including gender, age, race, ECOG PS, the type of platinum salt used, brain metastasis, liver metastasis, smoking status, LDH level and PD-L1 expression level. Through this analysis, we can screen out the population that is more suitable for first-line chemoimmunotherapy, which will make a great contribution to guiding the clinical treatment of ES-SCLC. Then, we conducted a subgroup analysis of the efficacy of different chemoimmunotherapy regimens in ES-SCLC patients of each group with clinical characteristics, including CTLA-4 inhibitors plus chemotherapy, PD-L1 inhibitors plus chemotherapy and PD-1 inhibitors plus chemotherapy. Therefore, we can select the dominant population of different chemoimmunotherapy, which can guide the precise clinical treatment of ES-SCLC.

Sensitivity analysis: Sensitivity analysis was performed using a "one study deletion" approach which can determine the sensitivity of the meta-analysis for each results. The results of some trials were inconsistent with the majority, which affected whether the overall results were statistically significant, so we performed sensitivity analyses on gender subgroup, PD-L1 expression level subgroup, brain metastasis subgroup, and liver metastasis subgroup.

Country(ies) involved: China.

Keywords: Efficacy heterogeneity, chemoimmunotherapy, extensive-stage small cell lung, Meta-analysis, systematic review.

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