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Immunotherapy efficacy of lung cancer and smoke: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - Key Project of the Affiliated Hospital of North Sichuan Medical College (2023ZD008).

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 November 2023 and was last updated on 14 November 2023.

INTRODUCTION

Review question / Objective P: Non-surgical, non-radiotherapy lung cancer patients receiving first-line chemotherapy or immunotherapy or chemotherapy combined with immunotherapy
I: smoking or former smoking
C: never smoke
O: HR of overall survival
S: RCT.

Condition being studied Although smoking is an important risk factor for lung cancer, previous studies suggest that lung cancer patients who smoke may benefit from immunotherapy, which is contradictory to the current belief that lung cancer patients should quit smoking. We did a systematic review and meta-analysis to assess the heterogeneity of immune checkpoint inhibitor efficacy between patients with smoking or former smoking and never smokers.

METHODS

Search strategy We searched PubMed, MEDLINE, Embase, and Scopus for phase 2 and 3 randomized controlled trials published from the inception of each database to Oct 31, 2023. We also reviewed abstracts and presentations from all major conference proceedings, including the American Society of Clinical Oncology and the European Society for Medical Oncology, from Jan 1, 2000, to Oct 31, 2023. Two investigators (LDC and CD) independently searched the databases. The search terms were "PD-1", "programmed death receptor 1", "immune checkpoint inhibitor", "ipilimumab", "tremelimumab", "nivolumab", "serplulimab" , "Durvalumab", "tislelizumab", "atezolizumab", "camrelizumab", "toripalimab", "sintilimab", "sugemalimab", "penpulimab" and "pembrolizumab". We also reviewed the references of articles included in the final selection.

Participant or population Non-surgical, non-radiotherapy lung cancer patients receiving first-line chemotherapy or immunotherapy or chemotherapy combined with immunotherapy.

Intervention Smoking or former smoking.

Comparator Never smoke.

Study designs to be included RCT.

Eligibility criteria All phase 2 and 3 randomised controlled trials in which immunological compounds were administered alone or in combination with chemotherapy, compared with chemotherapy.To be eligible, randomised trials had to assess inhibitors of PD-1, or their combination, in patients with lung cancer, and had to have data available for the hazard ratio (HR) for death according to smoke. We excluded single-arm phase 1 and 2 trials (ie, non-randomised trials), and one randomised controlled trial that reported overall survival data with a single PD-L1 inhibitor, to avoid excessive heterogeneity.

Information sources We searched PubMed, MEDLINE, Embase, and Scopus for phase 2 and 3 randomised controlled trials published from the inception of each database to Oct 31, 2023. We also reviewed abstracts and presentations from all major conference proceedings, including the American Society of Clinical Oncology and the European Society for Medical Oncology, from Jan 1, 2000, to Oct 31, 2023.

Main outcome(s) The primary endpoint was the difference in efficacy of immune checkpoint inhibitors between patients with smoking or former smoking and never smokers, measured in terms of the difference of the overall survival log(HR) reported in patients with smoking or former smoking and in never smokers.

Quality assessment / Risk of bias analysis We assessed the methodological quality of studies (to ascertain risk of bias) using the Cochrane Risk of Bias Tool.

Strategy of data synthesis We derived the HRs for death in the intervention group and control group, and their 95% CIs from each study, separately for patients with smoking or former smoking and never smokers. We calculated the pooled HR of death in patients with smoking or former smoking and never smokers using randomeffects models. We assessed the heterogeneity between the two estimates using an interaction test, to give pheterogeneity. We did the Q-test to assess between-study heterogeneity, and calculated the I^2 statistic, which expresses the percentage of the total observed variability due to study heterogeneity. To avoid the risk of ecological bias, we tested the null hypothesis (that the difference of immunotherapy effect between patients with smoking or former smoking and never smokers is zero) using the following approach: first, for each trial, we calculated an interaction trial-specific HR from the ratio of the reported HRs in patients with smoking or former smoking and in never smokers; second, we combined these trial-specific interaction HRs across trials using a random-effects model.

Subgroup analysis We did subgroup analyses to explore the variation of the effect of smoking state on immunotherapy efficacy. The subgroups were cancer histotype, smoking state,type of immune checkpoint inhibitor considered in the intervention group, and type of control group. We only considered subgroups including more than two studies. The null hypothesis, that the interaction between sex and immunotherapy efficacy is equal across subgroups, was tested with a χ^2 test.

Sensitivity analysis We conducted sensitivity analyses by dropping one study at a time and examining its influence on the summary effect estimates.

Language restriction English.

Country(ies) involved China.

Keywords lung cancer, smoke, immune checkpoint inhibitors.

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