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Comparing the efficacy and safety of perioperative immunotherapy combinations for resectable non-small cell lung cancer: a systematic review and network meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

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 08 August 2023 and was last updated on 08 August 2023.

INTRODUCTION

Review question / Objective After undergoing surgical resection for resectable non-small cell lung cancer (NSCLC), there is a significant risk of cancer recurrence. Several randomized clinical trials (RCTs) have investigated different combinations of perioperative immunotherapy and chemotherapy (IO-CT) regimens, including both neoadjuvant and adjuvant therapy. Understanding the clinical efficacy and safety profile of these IO-CT regimens is necessary for treatment strategy in clinical practice. To assess the differences between IO-CT and placebo-chemotherapy (PRO-CT) regarding efficacy and safety shown in RCTs focusing on perioperative IO-CT regimens, and find the optimal drug combination for perioperative therapy.

Condition being studied According to Cancer Statistics 2023, lung cancer remains the most deadly cancer in the world, and its incidence is second only to prostate cancer and breast cancer in men and women, respectively, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of primary lung cancer. The main goal of these patients with early and locally advanced resectable NSCLC is the cure, and encouraging results of clinical studies related to perioperative systemic therapy for patients with resectable NSCLC. Thus, there is an urgent need to identify more optimal perioperative chemo-exempt combination regimens for this specific subpopulation to guide clinical efforts and subsequent head-to-head clinical study design.

METHODS

Participant or population Patients with resectable non-small cell lung cancer using perioperative immunotherapy-chemotherapy or placebo-chemotherapy.

Intervention Pre-surgery neoadjuvant immunotherapy combined with chemotherapy, followed by surgery and post-surgery adjuvant therapy.

Comparator Pre-surgery neoadjuvant placebo-chemotherapy, followed by surgery and post-surgery adjuvant therapy/observation.

Study designs to be included All reported RCTs that focused on the comparison of perioperative immunotherapy-chemotherapy with placebo-chemotherapy were selected as candidates.

Eligibility criteria Papers meeting the following criteria were included based on the PICOS framework: (I) Only patients with early and locally advanced resectable NSCLC were considered. (II) Studies that focused on the comparison of perioperative immunotherapy-chemotherapy (IO-CT) with placebo-chemotherapy (PRO-CT) were included. (III) Studies that reported any of the following outcomes: pathologic complete response (pCR), major pathologic response (MPR), any-grade treatment-related adverse events (TRAEs), TRAEs of grade greater than or equal to 3, any-grade immune-related adverse events(irAEs), irAEs of grade greater than or equal to 3, event-free survival (EFS) and overall survival (OS). (V) All the included studies were RCTs. Exclusion criteria were as follows: (I) Patients with prior systemic immunosuppressive therapy or active autoimmune disease were excluded. (II) Studies that included radiotherapy interventions were excluded. (III) Case-control studies, retrospective studies, cohort studies, case reports, meta-analysis, and systematic reviews were also excluded. All included trials were reviewed online to ensure the inclusion of the most up-to-date data.

Information sources A comprehensive search for all RCTs related to NSCLC in databases including PubMed, Embase, and the Cochrane Library, spanning from the establishment of these databases up to July 2023. Manual searches for reviews, abstracts, and conference reports from major international lung cancer conferences.

Main outcome(s) The primary outcome was event-free survival (EFS). EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause.

Additional outcome(s) Overall survival (OS), major pathologic response (MPR), pathologic complete response (pCR), treatment-related adverse events (TRAEs) at any level, TRAEs greater than or equal to level 3, immune-related adverse events (irAEs) at any level, and irAEs greater than or equal to level 3.

Quality assessment / Risk of bias analysis The quality of the included studies was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (2.0). This evaluation considered factors such as randomization, double-blindness, completeness of outcome data, and selective reporting bias. The risk of bias was classified into three categories: low risk, high risk, and some concerns. Two authors independently conducted the quality evaluation of the included studies. Any disagreements were resolved through active discussion.

Strategy of data synthesis Effect sizes for EFS and OS were HRs with corresponding 95% CIs, while dichotomous variables used odds ratio (ORs) with corresponding 95% CIs. Statistical heterogeneity was assessed using the $\chi 2$ test and I2 statistic. A fixed-effects model was chosen if $\chi 2$ p-value >0.1 or I2 <50% for pooled estimates. If not, a random-effects model will be used. Statistically insignificant differences are indicated when the 95% CI for comparisons encompasses 1. The NMA employed a Bayesian framework to indirectly compare various IO-CT regimens with PRO-CT regimens. Four Markov chains with distinct initial values were executed in parallel for 100,000 iterations. Model convergence and diagnostic visualizations were obtained.We ranked the effectiveness and safety of the schemes using the area under the cumulative ranking curve (SUCRA). Schemes with higher SUCRA values (close to 1) indicated better effectiveness, while lower values (close to 0) indicated poorer effectiveness. Subgroup analyses were conducted based on predetermined factors, including PD-L1 expression level, disease stage at baseline, and histology. Publication bias was assessed using funnel plots and Egger tests ($p < 0.10$ indicating significant asymmetry). Sensitivity analysis was performed by sequentially excluding one study at a time to validate the results of the meta-analysis. Statistical analysis was performed using R software (version 4.3.0) and R Studio, with the incorporation of the gemtc and rjags packages.

Two-sided p-values were used, and statistical significance was defined as $p < 0.05$.

Subgroup analysis Subgroup analyses were conducted based on predetermined factors, including PD-L1 expression level, disease stage at baseline, and histology.

Sensitivity analysis Sensitivity analysis was performed by sequentially excluding one study at a time to validate the results of the meta-analysis.

Country(ies) involved China.

Keywords Perioperative; resectable; NSCLC; non-small cell lung cancer; immunotherapy; network meta-analysis.

Contributions of each author

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Author 2 - Hedong Han - Concept and design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding.
Author 3 - Suhua Zhu - Concept and design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content.
Author 4 - Chuling Li - Acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content.
Author 5 - Huijuan Li - Acquisition, analysis, or interpretation of data; statistical analysis.
Author 6 - Zhaofeng Wang - Acquisition, analysis, or interpretation of data; statistical analysis.
Author 7 - Ranpu Wu - Acquisition, analysis, or interpretation of data; drafting of the manuscript.
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