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kpoint Inhibitors Combined with Radiotherapy or Chemoradiotherapy for Advanced Non-Small Cell Lung Cancer: A Systematic Review and Single-Arm Meta-Analysis V.3

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Abstract

Background: The recent usage of immunotherapy combined with chemoradiotherapy has improved survival in advanced non-small cell lung cancer (NSCLC) patients. However, determining the most effective therapy combination remains a topic of debate. Research suggests immune checkpoint inhibitors (ICIs) post-chemoradiotherapy enhance survival, but the impact of concurrent ICIs during chemoradiotherapy on rapid disease progression is unclear. This meta-analysis aims to assess the effectiveness and safety of concurrent ICIs with radiotherapy or chemoradiotherapy in advanced non-small cell lung cancer.
Methods: We searched PubMed, Embase, the Cochrane Library, and Web of Science for relevant studies, extracting data on overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs).
Results: The analysis included ten studies with 490 participants. Stage III NSCLC ORR was 81.8%, while Stage IV ORR was 39.9%. One-year PFS and OS for Stage III were 68.2% and 82.6%, compared to 27.9% and 72.2% for Stage IV. Common adverse events included anemia (46.6%), nausea (47.6%), rash (36.4%), and radiation pneumonitis (36.3%).
Conclusions: Our meta-analysis shows concurrent ICIs with chemoradiotherapy are effective and safe in advanced NSCLC, particularly in stage III patients at risk of progression before starting ICIs after chemoradiotherapy. The findings support further phase III trials. The review protocol was registered on PROSPERO (CRD42023493685) and is detailed on the NIHR HTA programme website.

Attachments

Figures.rar
7.5MB

Supplementary.rar
37.4MB

Date and Statistical...
83KB

Guidelines

1. Study Design: This meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparent and comprehensive reporting of the study methods and results.
2. Literature Search: A comprehensive literature search will be conducted using multiple electronic databases (PubMed, Embase, Cochrane Library, and Web of Science) to identify all relevant studies. The search strategy will be developed in consultation with a medical librarian and will include a combination of MeSH terms and free-text keywords.
3. Study Selection: Two independent reviewers will screen the titles and abstracts of the retrieved articles for relevance. Full-text articles will be assessed for eligibility based on the predefined inclusion and exclusion criteria. Any discrepancies will be resolved through discussion or consultation with a third reviewer.
4. Data Extraction: Two independent reviewers will extract data from the included studies using a standardized data extraction form. The extracted data will include study characteristics (e.g., author, year, study design, sample size), patient demographics, treatment details (e.g., type of ICI, radiotherapy dose, chemotherapy regimen), and outcomes (e.g., ORR, PFS, OS, AEs).
5. Quality Assessment: The quality of the included studies will be assessed using appropriate tools based on the study design. The Cochrane Risk of Bias Tool will be used for randomized controlled trials, while the Newcastle-Ottawa Scale will be used for non-randomized studies. Two independent reviewers will perform the quality assessment, and discrepancies will be resolved through discussion.
6. Statistical Analysis: The meta-analysis will be conducted using a random-effects model to account for heterogeneity among the included studies. Heterogeneity will be assessed using the I^2 statistic and Cochran's Q test. Subgroup analyses will be performed based on factors such as tumor stage, type of ICI, and type of radiotherapy. Sensitivity analyses will be conducted to evaluate the robustness of the results. Publication bias will be assessed using funnel plots and Egger's test.
7. Interpretation of Results: The results of the meta-analysis will be interpreted in the context of the available evidence and the limitations of the included studies. The clinical implications of the findings will be discussed, and recommendations for future research will be provided.

Materials

Search Strategy

Four databases – PubMed, Embase, the Cochrane Library, and Web of Science – were thoroughly searched for pertinent studies. The final search date was 4 January 2024. The search strategy incorporated both MeSH terms and free-text words: "concurrent radiotherapy" OR "concurrent radiation therapy" OR "concurrent chemoradiotherapy" OR "concurrent radiotherapy AND immunotherapy" OR "concurrent chemoradiotherapy AND immunotherapy" AND ("immune checkpoint inhibitors" OR "PD-1 inhibitors" OR "PD-L1 inhibitors" OR "CTLA-4 inhibitors" OR "immune modulation" OR "immunotherapy") AND "advanced NSCLC" OR "advanced non-small cell lung cancer". Searches were restricted to English language publications. Additionally, the references of the included articles were reviewed to identify further relevant studies.

Selection Criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: 1) population: patients diagnosed with advanced non-small cell lung cancer (NSCLC); and 2) intervention: patients treated with concurrent immune checkpoint inhibitors (ICIs) combined with radiotherapy/chemoradiotherapy. Study Type: Prospective interventional research, retrospective analyses, or randomized controlled trials (RCTs). 3) Outcomes: Clinical tumor outcomes of interest, including objective response rate (ORR), one-year progression-free survival (PFS), one-year overall survival (OS), and adverse events (AEs), were reported. 4) Tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) [19], version 1.1. Toxic effects were assessed for incidence and severity using the Common Terminology Criteria for Adverse Events (CTCAE). The exclusion criteria were as follows: Animal-related studies, cell studies, reviews, meta-analyses, duplicates, case reports, or letters.

Two investigators independently screened the articles for eligibility using the inclusion and exclusion criteria. Any disagreements regarding study selection were resolved by discussion between the two investigators or with the involvement of a third investigator.

Data Extraction and Quality Assessment

Data from all included studies were independently extracted by two investigators, who also conducted a quality assessment of the studies. The extracted data included author name, publication year, study type, sample size, intervention, tumor stage, median follow-up time, EGFR mutation status, and reported endpoints. Clinical and safety outcomes were evaluated based on the overall response rate (ORR), one-year overall survival (OS), one-year progression-free survival (PFS), incidence of any adverse events (AEs), and incidence of grade 3 or higher AEs.

Furthermore, the quality of the included randomized controlled trials (RCTs) was assessed using the Jadad scale, while the retrospective studies were evaluated using the Joanna Briggs Institute Critical Appraisal Checklist for Patient Series. The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the included noncontrolled trials.

Statistical Analysis

This meta-analysis was conducted using STATA 17 software (StataCorp LP, College Station, TX, United States) to analyze the data. Heterogeneity among studies was assessed with the chi-square test and I2 statistic, with p values less than 0.1 denoting significant differences. In cases where there was significant variability ($p < 0.1$ and $I2 > 50\%$), the analysis utilized a random effects approach. On the other hand, for scenarios with lower variability, a fixed-effects approach was chosen. Additionally, sensitivity analyses were conducted to assess the robustness and reliability of the findings. The potential for publication bias was examined through the application of Begg's and Egger's tests.

Safety warnings

1. Adverse Events: Combining immune checkpoint inhibitors with radiotherapy or chemoradiotherapy may increase the risk of adverse events, particularly immune-related adverse events (irAEs) such as pneumonitis, colitis, and endocrinopathies . Patients should be closely monitored for signs and symptoms of irAEs, and prompt management should be initiated according to established guidelines .
2. Radiation Dose and Volume: The radiation dose and volume should be carefully considered when combining radiotherapy with immune checkpoint inhibitors, as higher doses and larger volumes may increase the risk of toxicity . The optimal radiation dose and fractionation schedule for use with immune checkpoint inhibitors are still under investigation, and caution should be exercised when deviating from established protocols.
3. Timing of Immune Checkpoint Inhibitor Administration: The timing of immune checkpoint inhibitor administration relative to radiotherapy or chemoradiotherapy may impact the efficacy and safety of the combination . While concurrent administration has shown promise in some studies, it may also increase the risk of adverse events. The optimal timing of immune checkpoint inhibitor administration should be based on available evidence and patient-specific factors.
4. Patient Selection: Careful patient selection is crucial when combining immune checkpoint inhibitors with radiotherapy or chemoradiotherapy, as certain patient populations may be at higher risk of adverse events. Patients with pre-existing autoimmune disorders, prior history of severe irAEs, or compromised organ function should be evaluated on a case-by-case basis, and the potential benefits of the combination should be weighed against the risks .
5. Long-term Follow-up: As the use of immune checkpoint inhibitors in combination with radiotherapy or chemoradiotherapy is a relatively new approach, long-term follow-up data on the safety and efficacy of these combinations are limited . Patients should be informed of the potential for late-onset adverse events and the need for ongoing monitoring even after the completion of treatment.

Ethics statement

This meta-analysis was conducted in accordance with the Declaration of Helsinki. All included studies had obtained informed consent from their participants and were approved by their respective institutional ethics committees. As this study is a meta-analysis of previously published data, no additional informed consent was required.

Before start

Protocol Registration: The study protocol should be registered in a publicly accessible database, such as PROSPERO (International Prospective Register of Systematic Reviews) or the Open Science Framework (OSF), to promote transparency and reduce duplication of efforts.

Search Strategy Development: The search strategy should be developed in consultation with a medical librarian or an information specialist to ensure that it is comprehensive and captures all relevant studies. The search strategy should be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [23] to minimize errors and improve its effectiveness.

Data Management: A data management plan should be established before starting the study to outline how data will be collected, stored, and shared. This plan should include measures to ensure data security, confidentiality, and access control. The use of a secure, cloud-based platform, such as REDCap (Research Electronic Data Capture) [24], can facilitate efficient and secure data management.

Study Protocol: The study protocol should be developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines to ensure that all essential elements are included. The protocol should be reviewed and approved by all members of the research team before the start of the study.

Authorship and Collaboration: The roles and responsibilities of each member of the research team should be clearly defined, and authorship criteria should be established in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines . If the meta-analysis involves collaboration with external partners or institutions, data sharing agreements and memoranda of understanding should be established to ensure smooth collaboration and protect intellectual property rights.

Training and Calibration: All members of the research team should receive appropriate training on the study protocol, data extraction, quality assessment, and statistical analysis methods to ensure consistency and minimize errors. Calibration exercises should be conducted to assess inter-rater reliability and resolve any discrepancies in the interpretation of the study criteria.

steps

1 Develop a research question and hypothesis:Clearly define the research question and hypothesis for the meta-analysis, focusing on the efficacy and safety of concurrent immune checkpoint inhibitors combined with radiotherapy or chemoradiotherapy for advanced non-small cell lung cancer.

2 Register the protocol: Register the study protocol in a publicly accessible database, such as PROSPERO or the Open Science Framework, to promote transparency and reduce duplication of efforts.

3 Develop a search strategy: In consultation with a medical librarian or information specialist, develop a comprehensive search strategy that captures all relevant studies. Peer-review the search strategy using the PRESS checklist.

4 Conduct a literature search: Search multiple electronic databases (PubMed, Embase, Cochrane Library, and Web of Science) using the developed search strategy to identify all relevant studies.

5 Screen and select studies: Two independent reviewers should screen the titles and abstracts of the retrieved articles for relevance. Assess full-text articles for eligibility based on the predefined inclusion and exclusion criteria. Resolve any discrepancies through discussion or consultation with a third reviewer.

6 Extract data: Two independent reviewers should extract data from the included studies using a standardized data extraction form. Extract study characteristics, patient demographics, treatment details, and outcomes.

7 Assess study quality: Assess the quality of the included studies using appropriate tools based on the study design (e.g., Cochrane Risk of Bias Tool for randomized controlled trials, Newcastle-Ottawa Scale for non-randomized studies). Two independent reviewers should perform the quality assessment and resolve discrepancies through discussion.

8 Conduct statistical analysis: Perform meta-analysis using a random-effects model to account for heterogeneity among the included studies. Assess heterogeneity using the I^2 statistic and Cochran's Q test. Perform subgroup analyses based on factors such as tumor stage, type of ICI, and type of radiotherapy. Conduct sensitivity analyses to evaluate the robustness of the results. Assess publication bias using funnel plots and Egger's test.

9 Interpret results: Interpret the results of the meta-analysis in the context of the available evidence and the limitations of the included studies. Discuss the clinical implications of the findings and provide recommendations for future research.

10 Draft the manuscript: Write the manuscript following the PRISMA guidelines, including all essential elements such as the abstract, introduction, methods, results, discussion, and

conclusion. Ensure that the manuscript adheres to the journal's formatting and submission requirements.

11 Review and revise: Circulate the draft manuscript among all authors for review and feedback. Revise the manuscript based on the comments and suggestions received.

12 Submit for publication: Submit the final manuscript to the target journal and respond to any reviewer comments or editorial requests during the peer-review process.

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