INPLASY

The ICI-based therapy landscape in resectable non-small cell lung cancer: a comparative analysis of treatment efficacy and safety between neo-adjuvant, adjuvant and perioperative immunotherapy

INPLASY2023100084

doi: 10.37766/inplasy2023.10.0084

Received: 26 October 2023

Published: 26 October 2023

Wang, YY[1]; Zhang, L[2]; Liu, Y[3]; Zhou, HQ[4]; Yu, H[5]; Li, AL[6]; Liu, TT[7]; Sun, DC[8]; Hong, SD[9]; Fang, WF[10]; Li,J[11]; Zhang, L[12]; Yang, YP[13].

Corresponding author:
Yuanyuan Wang

wangyy4@sysucc.org.cn

Author Affiliation:
Department of Medical Oncology, Sun Yat-Sen University Cancer CenterSun Yat-Sen University Cancer Center.

ADMINISTRATIVE INFORMATION

Support - The National Natural Science Foundation of China (Grant No. 82072558）.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2023100084

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 October 2023 and was last updated on 26 October 2023.

INTRODUCTION

Review question / Objective Patient: the patients with resectable non-small cell lung cancer; Intervention: neo-adjuvant, adjuvant and perioperative immunotherapy versus chemotherapy comparison: neo-adjuvant, adjuvant and perioperative immunotherapy Outcome: event-free survival (EFS), overall survival (OS), objective response rate (ORR), pathology complete response (pCR), major pathological response rate (MPR), treatment-related adverse events (TRAEs) and postoperative complications; Study: Published and unpublished randomised controlled trials comparing two or more treatments.

Rationale The aim of this study is to compare the efficacy and safety of neoadjuvant immunotherapy, adjuvant immunotherapy, and perioperative immunotherapy and to develop optimal treatment regimens for perioperative NSCLC patients with different clinical characteristics.

Condition being studied For over ten years, thoracic oncologists have made great strides in the treatment of patients with non-small cell lung cancer (NSCLC). However, the 5-year overall survival (OS) rates for patients with localized Stage II or localized Stage III NSCLC are still low, with between thirty and fifty percent of patients dying of lung cancer after undergoing radical surgery. Patients with a high risk of recurrence are advised to follow neoadjuvant/adjuvant chemotherapy regimens; nevertheless, these treatments have not significantly improved 5-year OS (about 5% improvement in 5-year survival). Therapeutic strategies that utilize the immune system to eliminate tumor cells have been successfully used in patients with many types of tumors, including advanced non-small cell lung cancer (NSCLC). In these patients, immune checkpoint inhibitors (ICIs) in combination with chemotherapy can provide durable responses and improve overall survival

compared to neoadjuvant or adjuvant chemotherapy alone.

The CheckMate-816 study stuns with a nearly 11-fold benefit in pCR rate and unveils a neoadjuvant immunotherapy milestone for non-small cell lung cancer (NSCLC) prologue. The IMpower010 and KEYNOTE-091 trials have also demonstrated the benefit of adjuvant immunotherapy (IO) after chemotherapy (C+IO) in resected non-small cell lung cancer (NSCLC). With the recent spate of full perioperative management modalities combining neoadjuvant and adjuvant immunotherapy, a question arises: which of the three immunotherapy modalities is superior?

METHODS

Search strategy The search terms used in PubMed was ("non-small-cell lung cancer" [title] OR "non-small cell lung cancer" [title] OR "non small-cell lung cancer" [title] OR "non small cell lung cancer" [title] OR "non-small-cell lung carcinoma" [title] OR "non-small cell lung carcinoma" [title] OR "non small-cell lung carcinoma" [title] OR "non small cell lung carcinoma" [title] OR "nsclc" [title]) AND ("adjuvant"[Title/Abstract] OR "neoadjuvant"[Title/Abstract] OR "perioperative"[Title/Abstract] OR "resectable"[Title/Abstract]) AND ("ipilimumab"[Title/Abstract] OR "tremelimumab"[Title/Abstract] OR "nivolumab"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "durvalumab"[Title/Abstract] OR "Toripalimab"[Title/Abstract] OR "Tislelizumab"[Title/Abstract] OR "Camrelizumab"[Title/Abstract] OR "Sintilimab"[Title/Abstract] OR "Sugemalimab"[Title/Abstract] OR "Envafolimab"[Title/Abstract] OR "immunotherapy"[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract] OR "programmed cell death protein 1"[Title/Abstract] OR "programmed cell death protein"[Title/Abstract] OR "PD-1"[Title/Abstract] OR "programmed cell death ligand 1"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR "cytotoxic t lymphocyte associated antigen 4"[Title/Abstract] OR "CTLA-4"[Title/Abstract] OR "CTLA4"[Title/Abstract]) AND "chemotherapy"[Title/Abstract] AND ("plus"[Title/Abstract] OR "versus"[Title/Abstract] OR "compare"[Title/Abstract] OR "comparison"[Title/Abstract] OR "comparative"[Title/Abstract] OR "comparing"[Title/Abstract] OR "Trial"[Title/Abstract] OR "phase"[Title/Abstract] OR "randomized controlled trials"[Title/Abstract]) AND ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "Randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "randomly"[Title/Abstract] OR "Trial"[Title/Abstract] OR "phase"[Title/Abstract]) AND "English"[Language] AND "humans"[MeSH Terms].

Participant or population Inclusion: ECOG PS 0 or 1, resectable NSCLC stage IB, II, IIIA, or selected IIIB.

Intervention Neo-adjuvant, adjuvant, perioperative immunotherapy and chemotherapy.

Comparator Neo-adjuvant, adjuvant and perioperative immunotherapy.

Study designs to be included Published and unpublished randomised controlled trials comparing two or more treatments.

Eligibility criteria Studies were included if they (1) were randomized clinical head-to-head phase 2 or 3 trials; (2) enrolled patients with either histologically or pathologically confirmed resectable NSCLC; (3) compared 2 or more treatments for patients with NSCLC, including chemotherapy and any of neo-adjuvant, adjuvant or perioperative immunotherapy regimen. (4) reported detailed outcomes and toxic effects including event free survival (EFS), overall survival (OS), objective response rate (ORR), pathology complete response (pCR), major pathological response rate (MPR), treatment related adverse events (TRAEs) of grade 3 or higher and postoperative complications; Studies failing to meet these criteria were excluded.

Information sources PubMed, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and several international conference databases, from inception to October 25, 2023.

Main outcome(s) Event-free survival (EFS), pathology complete response (pCR), major pathological response rate (MPR), treatment-related adverse events (TRAEs) and postoperative complications.

Additional outcome(s) Overall survival (OS), objective response rate (ORR).

Quality assessment / Risk of bias analysis We used the Cochrane collaboration's tool for assessing the risk of bias. Its methodology bias assessment includes six items: random sequence generation, allocation concealment, blinding,

incomplete outcome data, selective outcome reporting, and other sources of bias. The evaluation level of each item includes "high risk", "low risk" or "unclear".

Strategy of data synthesis We integrated all data and performed this meta-analysis using Review Manager 5.3 software. The integrated data included the primary outcome and secondary outcomes. We used Cochrane's Q statistic to assess between-study heterogeneity and calculated the I2 statistic, which estimates the percentage of total variation across studies due to heterogeneity rather than chance. The pooled estimates for PFS and OS were presented with HRs, 95% CIs, and P values calculated using the inverse variance-weighted method. The dichotomous variables (ORR and frequency of adverse events) were pooled with the risk ratios (RRs), 95% CIs, and P values using the Mantel-Haenszel method. The random effect models were chosen if obvious heterogeneity was present (I2 > 50%); otherwise, the fixed effect models were applied.

Subgroup analysis The subgroups include pathological stage, ECOG PS (0 or 1), age, and different TRAEs. Subgroup analysis was performed using the same strategy as the overall population.

Sensitivity analysis Sensitivity analysis will be done if needed.

Language restriction English.

Country(ies) involved China.

Keywords Neoadjuvant therapy、adjuvant therapy、immunotherapy, perioperative、non–small cell lung cancer, randomized controlled trial、chemotherapy.

Contributions of each author

Author 1 - Yuanyuan Wang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft preparation, Writing –reviewing and editing.
Email: wangyy4@sysucc.org.cn
Author 2 - Lin Zhang: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing –Original draft preparation.
Email: zhanglin2@sysucc.org.cn
Author 3 - Yu Liu: Data curation, Investigation, Methodology, Visualization, Writing – reviewing and editing.
Email: liuyu@sysucc.org.cn
Author 4 - Huaqiang Zhou: Data curation, Investigation, Methodology, Visualization, Writing – reviewing and editing.
Email: zhouhq@sysucc.org.cn
Author 5 - Hui Yu - HuiYu: Data curation, Investigation, Methodology, Visualization, Writing – reviewing and editing.
Email: yuhui1@sysucc.org.cn
Author 6 - Anlin Li : Data curation, Investigation, Methodology, Visualization, Writing – reviewing and editing.
Email: lial@sysucc.org.cn
Author 7 - Tingting Liu: Data curation,Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: liutt@sysucc.org.cn
Author 8 - Dongchen Sun: Data curation,Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: sundc@sysucc.org.cn
Author 9 - Shaodong Hong: Data curation,Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: fangwf@sysucc.org.cn
Author 10 - Wenfeng Fang: Data curation,Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: fangwf@sysucc.org.cn
Author 11 - Jing Li：Conceptualization, Resources, Supervision, Funding acquisition, Data curation, Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: lijing3@sysucc.org.cn
Author 12 - Li Zhang：Conceptualization, Resources, Supervision, Funding acquisition, Data curation, Investigation, Methodology, Validation, Writing – reviewing and editing.
Email: zhangli@sysucc.org.cn
Author 13 - YunpengYang：Conceptualization, Resources, Supervision, Funding acquisition, Data curation, Investigation, Methodology, Validation, Writing –reviewing and editing.
Email: yangyp@sysucc.org.cn