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Network meta-analysis of first-line therapy for NSCLC patients with liver metastases: Implications for improving prognosis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

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 12 August 2024 and was last updated on 12 August 2024.

INTRODUCTION

Review question / Objective The liver is the most common location of metastatic lesions in patients with non-small cell lung cancer (NSCLC), and the presence of liver metastasis (LMs) is a strong predictor of poor outcomes. Therefore, determining the optimal first-line treatment for this condition is of great importance to improve patient survival and overall prognosis. The primary objective of this study was to determine the most effective first-line treatment option for liver metastases arising from NSCLC.

Condition being studied Lung cancer remains the most common malignancy worldwide and the leading cause of cancer-related mortality, with non-small cell lung cancer (NSCLC) accounting for approximately 80% of all cases [1]. At initial diagnosis, more than 30% of NSCLC cases are at an advanced stage, precluding curative local treatment options. Of these, liver metastases (LMs) occur in approximately 15-20% of patients at diagnosis and up to 28-33% during disease progression, and are an independent poor prognostic factor for survival [2, 3]. Compared to other metastatic sites such as the brain or bone, patients with liver metastases have the highest risk of death, with median overall survival (OS) of only 3-5 months and a 5-year OS rate of only 1-2.2% [4, 5]. Survival rates are significantly lower in patients with multiple or concomitant liver metastases [6]. Traditional chemotherapy offers these patients a median survival of approximately 6 months, presenting a major clinical challenge.

Given the expanding armamentarium of ICIs and the growing evidence supporting different immunotherapy combinations, there is an urgent need to clarify whether different ICIs and combined strategies have different efficacy in the treatment of NSCLC with liver metastases. To address this clinical dilemma, we conducted a network meta-

analysis (NMA) to identify the optimal frontline therapeutic strategy for this subset of NSCLC patients characterized by an exceptionally poor prognosis, with the aim of informing clinical practice.

METHODS

Participant or population The study population was advanced inoperable NSCLC with LMs and non-LMs.

Intervention Included an intervention comparing treatments between different combinations including PD-1/PD-L1 or CTLA-4 immune checkpoint inhibitors, bevacizumab or chemotherapy etc.

Comparator Chemotherapy, bevacizumab combine with chemotherapy, and PD-L1 combine with chemotherapy.

Study designs to be included Randomized controlled trials.

Eligibility criteria (1) focused on patients with advanced, first-line, unresectable NSCLC; (2) reported survival outcomes, including median PFS and median OS, along with hazard ratios (HR) and corresponding 95% confidence intervals specifically for subgroups with and without liver metastases; (3) were prospective RCTs; and (4) included both an intervention and a control group comparing treatments between different combinations including PD-1/PD-L1 or CTLA-4 immune checkpoint inhibitors, bevacizumab or chemotherapy etc.

Information sources Electronic databases.

Main outcome(s) Median PFS and median OS, along with hazard ratios (HR) and corresponding 95% confidence intervalsDescribe the outcomes of the review including all relevant details such as timing and effect measures.

Quality assessment / Risk of bias analysis The methodological quality of the included trials was rigorously assessed using the Cochrane risk of bias assessment tool integrated into the Review Manager 5.3 software. This assessment covered six critical areas: selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias.Publication bias was assessed using Egger's tests.

Strategy of data synthesis The primary outcomes of interest were OS and PFS, quantified as HRs with their respective 95% confidence intervals (CIs). Pairwise meta-analysis was performed to facilitate direct comparisons between interventions using STATA 17.0, and graphical representations of these comparisons were visualized using forest plots.
Network meta-analyses were performed with the statistic program R version 4.3.2 using the version 2.9.0“netmeta” package. We performed a network meta-analysis using the frequency count model. For each intervention, we applied the random effect model to generate the study effect sizes. We computed the network plot with the “netgraph” function from the “netmeta” package, the forest plot with "forest" function and the comparison-adjusted funnel plots with the function “funnel”. Each treatment therapy was ranked using the surface under the cumulative ranking curve (SUCRA), and a treatment hierarchy was generated. A treatment ranked 100% is certain to be the best, and a treatment ranked 0% is certain to be the worst. To assess the inconsistency between direct and indirect comparisons, we compared the pooled HRs from the network meta-analysis with corresponding HRs from traditional pair-wise random-effects meta-analysis of direct comparisons.

Subgroup analysis Network meta-analysis of OS in the LMs subgroup; Network meta-analysis of PFS in the LMs subgroup.

Sensitivity analysis Heterogeneity between trials was quantified using I-squared (I^2) statistics and P-values. High levels of heterogeneity were indicated by an I^2 value greater than 75%. In cases where heterogeneity was substantial ($I^2 \geq 75\%$), sensitivity analyses were performed to explore the robustness of the results under different assumptions and data exclusions.

Country(ies) involved China.

Keywords NSCLC; liver metastases; Network meta-analysis.

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