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Comparative effectiveness of first-line therapies for extensive-stage small cell lung cancer with liver metastases: A network meta-analysis and systematic review

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ADMINISTRATIVE INFORMATION

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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 07 June 2024 and was last updated on 07 June 2024.

INTRODUCTION

Review question / Objective This study aimed to compare the efficacy of first-line regimens of programmed cell death (or ligand) (PD-(L)1) blockade-based treatments in patients with SCLC with LM, and to explore the optimal treatment strategies for these patients.

Condition being studied Patients with extensive-stage small cell lung cancer (ES-SCLC) who develop liver-metastatic disease (LM) have very poor prognosis, and which chemo-immunotherapy (CIT) regimens best benefit these patients is unclear. This study aimed to compare the efficacy of first-line regimens of programmed cell death (or ligand) (PD-(L)1) blockade-based treatments in patients with SCLC with LM, and to explore the optimal treatment strategies for these patients.

METHODS

Participant or population Patients with extensive-stage small cell lung cancer.

Intervention Randomized controlled trials (RCTs) comparing CIT and chemotherapy (CT) in patients with ES-SCLC.

Comparator No applicable.

Study designs to be included Randomized controlled trials (RCTs) comparing CIT and chemotherapy (CT) in patients with ES-SCLC.

Eligibility criteria (1) randomized controlled trials (RCTs); (2) studies in treatment-naïve patients; (3) studies comparing survival outcomes (PFS and/or OS) in patients with ES-SCLC treated with first-line CTLA-4/PD-1/PD-L1 inhibitors (monotherapy or

combination strategies) versus CT; (4) studies reporting hazard ratios (HRs) for survival analysis (PFS or OS) or numbers of events for relevant clinical endpoints for subgroups stratified by LM status; and (5) studies reporting original data enabling calculation of HRs or p values.

Information sources PubMed, Embase, Web of Science, Cochrane Library, and ClinicalTrials.gov databases.

Main outcome(s) Survival outcomes (PFS and/ orOS).

Quality assessment / Risk of bias analysis Two reviewers (LS and JHZ) independently assessed the quality of the RCTs with the Cochrane Risk of Bias (RoB) 2 tool.13 Selection bias (random sequence generation, allocation concealment, blinding of patients and personnel, incomplete outcome data, selective reporting, and other biases) was also assessed. Disagreements among investigators were resolved by discussion with the other investigators.

Strategy of data synthesis Direct and indirect data were collected to compare the effectiveness of the treatments. Meta-analysis was performed in STATA version 14.0. HRs and 95% confidence intervals (CIs) for the PFS and OS in patients with ES-SCLC were calculated and presented in forest plots. Heterogeneity among the included studies was assessed with I2 values. If an I2 statistic >50% or p value < 0.05 indicated significant heterogeneity among the included studies, the random effects model was used for analysis. Otherwise, the fixed-effects model was used. Funnel plots, and Begg's and Egger's tests, were used to detect publication biases. In addition, leave-one-out sensitivity analysis was performed. All reported p-values are two-tailed, and a p-value below 0.05 was considered statistically significant.
R language (R version 4.3.2) was used for the network meta-analysis. Depending on the degree of heterogeneity, a fixed-effects model or random-effects model was selected, and consistency was tested with the node-splitting method. Finally, we evaluated the sequence of therapeutic effects according to rank probability plots, forest plots, league tables, and the area under the cumulative ranking curve. In assessment of the efficacy of PFS and OS indexes, an HR less than 1.0 was considered to indicate that the treatment was more beneficial to the patient than the other treatments. In indirect comparisons, a CI crossing 1.0 was considered to indicate no statistical significance.

Subgroup analysis Subgroup analysis according to anti-PD-1 or anti-PD-L1 treatmentPD-1.

Sensitivity analysis Sensitivity analysis was performed to assess the effects of each RCT on the pooled HRs of the median OS of patients with ES-SCLC with LM by sequential exclusion of each eligible study.

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Keywords Immunotherapy, liver metastases, meta-analysis, small cell lung cancer.

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