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Clinical Efficacy of Lenvatinib, Trans-arterial Chemoembolization, and PD-1/L1 Inhibitors in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - No.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202410065

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 January 2024 and was last updated on 16 January 2024.

INTRODUCTION

Review question / Objective This study employed a network meta-analysis to assess the efficacy and safety of trans-arterial chemoembolization (TACE), Programmed Cell Death Protein/Ligand 1 (PD-1/L1) inhibitors, and Lenvatinib in treating advancedHCC.

Condition being studied Lenvatinib is an FDA-approved drug and has been adopted in first-line treatment of liver cancer, resulting in an increasing use in clinical practice, especially in combination therapy regimens[10]. Programmed Cell Death Protein 1 (PD-1) or Programmed Cell Death Ligand 1 (PD-L1) inhibitors have been extensively used in the treatment of various malignancies and have become first- or second-line options for systemic treatment of advanced HCC due to promising efficacy for liver cancer substantiated by multiple clinical studies.

METHODS

Participant or population Patients with advanced hepatocellular carcinoma who were considered unsuitable for curative surgery; Eastern Cooperative Oncology Group (ECOG) score of 0-2; expected survival time of over 3 months; no prior systemic treatment.

Intervention / Comparator At least two treatment modalities, including either TACE, Lenvatinib, or PD-1/L1 inhibitors used as single treatments or in combination.

Study designs to be included A computer-based search was conducted in both Chinese and English databases, including PubMed, EMBASE, ClinicalTrials.gov, Cochrane Library, CNKI, and Wanfang, for literature on the treatment of advanced Hepatocellular Carcinoma (HCC) using TACE, PD-1/L1 inhibitors, and Lenvatinib.

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Eligibility criteria This study employed the criteria of study population, intervention measures, control measures, outcomes, and study design as the process for literature selection. Study Population: Patients with advanced hepatocellular carcinoma who were considered unsuitable for curative surgery; Eastern Cooperative Oncology Group (ECOG) score of 0-2; expected survival time of over 3 months; no prior systemic treatment.

Information sources After conducting a computer-based literature search and importing into Endnote, a total of 1352 articles were retrieved. 1352 relevant studies in initial search: PubMed (n=225), EMBASE (n=234), Clinical Trials gov (n=101), Cochrane Libraryand (n=211), CNKI (n=268), and Wanfang (n=313). After removing duplicates, 1126 articles remained. Following the inclusion and exclusion criteria, 1049 articles were excluded based on abstract readings, including 514 being non-clinical studies, 393 lacking specified intervention methods, and 142 being reviews or case reports. Full-text reading was conducted on the remaining 77 articles. Among them, 36 did not include specified outcome indicators and 20 had unclear diagnoses. After screening, 21 meta-analyses were included.

Main outcome(s) Objective Response Rate (ORR) and Disease Control Rate (DCR) based on modified Response Evaluation Criteria in Solid Tumors (mRECIST); Overall Survival (OS); Progression-Free Survival (PFS).

Additional outcome(s) According to WHO standards, it is classified as level 0-IV, with level 0 being normal and no response. Level IV is the most severe adverse reaction that can endanger life, such as gastrointestinal reactions, neurological reactions, cardiac reactions, skin reactions, hair loss reactions, body temperature, etc., all ranging from level 0-IV. Clinicians should closely observe adverse reactions to chemotherapy, and if moderate-to-severe reactions occur, they should be promptly and actively treated. Adverse Events (AEs) of grade 3 or higher.

Data management Two researchers independently extracted data from each study using a pre-specified Excel sheet (Microsoft Excel 2013, USA). A third investigator cross-checked the data, and any discrepancies were resolved through discussion. The extracted information included first author, publication year, study location (country and region), population type, sample size for each study group, sex, age, control interventions, intervention measures for each study group, and outcome indicators. In cases where specific data could not be extracted or were not clearly reported in the paper, the corresponding authors of the respective studies were contacted.

Quality assessment / Risk of bias analysis The quality of the included literature was assessed using the Cochrane recommended Cochrane Risk of Bias Assessment Tool, discussing bias sources based on seven dimensions, namely, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The risk was classified as high, uncertain, or low. The quality of included retrospective studies was assessed using the Newcastle-Ottawa Scale (NOS). Scores were assigned based on selection, comparability, and outcome, with a maximum score of 9, and studies with a score above 5 were considered high quality.

Strategy of data synthesis The meta-analysis was conducted using the R language package gemtc. Bayesian mesh meta-analysis using R language package gemtc. Hazard Ratios (HR) and 95% Confidence Intervals (CI) were analyzed for OS, PFS, and Time to Progression (TTP). Odds Ratios (OR) and their 95% CI were employed for ORR, DCR, and AEs. $P < 0.05$ was considered statistically significant. A total of 50,000 iterations were performed, with the initial 20,000 used for algorithm annealing to eliminate the influence of initial values. Forest plots were generated for result comparison, and Surface Under the Cumulative Ranking (SUCRA) values were predicted for the efficacy ranking of each intervention.

Subgroup analysis The SUCRA value ranges from 0 to 100%, with higher values indicating better intervention efficacy and higher ranking.

Sensitivity analysis The I2 test was used to explore heterogeneity, where I2.pair (Tauared) represents the degree of heterogeneity between adjacent study results, measuring the variance of bias between two study results, and I2.cons (I Squared) represents the degree of overall study result heterogeneity, measuring the variance of bias in all study results. In the network meta-analysis results, each point on the evidence network graph represents an intervention measure, and lines connecting points indicate direct comparisons between two intervention measures. The thickness of the line indicates the number of studies between the two intervention measures, and the size of the circle represents the total sample size of the intervention measure.

Country(ies) involved Guangzhou, China.

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Keywords Hepatocellular Carcinoma; Lenvatinib; Trans-arterial Chemoembolization; PD-1/L1 Inhibitors; Monotherapy; Combination Therapy.

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