INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Efficacy and safety of immune checkpoint inhibitor and anti-VEGF combination therapy in unresectable Hepatocellular carcinoma: a systematic review and meta-analysis

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Review question / Objective: **Recently, immune-checkpoint inhibitors combined with anti -VEGF combination therapy has been a new treatment option for patients with unresectable hepatocellular carcinoma. Our objective was to assess the comparative efficacy and safety of immune checkpoint inhibitor and anti-VEGF therapy combination therapy for advanced or metastatic hepatocellular carcinoma by a systematic review and networkmeta-analysis.**
Condition being studied: **Hepatocellular carcinomai s a common cancer worldwide and a importent cause of cancer-related death. Although several therapies are used in the first-line treatment of hepatocellular carcinoma, the clinical outcome of patients are still not Satisfactory.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 August 2021 and was last updated on 30 August 2021 (registration number INPLASY202180112).

INTRODUCTION

Review question / Objective: **Recently, immune-checkpoint inhibitors combined with anti -VEGF combination therapy has been a new treatment option for patients with unresectable hepatocellular carcinoma. Our objective was to assess the comparative efficacy and safety of immune checkpoint inhibitor and anti-VEGF therapy combination therapy for advanced or metastatic hepatocellular carcinoma by a**

systematic review and networkmeta-analysis.

Rationale: The multikinase inhibitors sorafenib and lenvatinib are the approved firstline systemic treatments for unresectable hepatocellular carcinoma. Recently, immune checkponit inhibitors have shown promising clinical activity in treatment for advanced hepatocellular carcinoma. Morever,the conbination of ICIs and anti-VEGF therapy also show promising efficacy in patients with hepatocellular carcinoma in some clinical trials. Our study aimed to invesitigate the efficacy and safety of ICI and anti-VEGF combination therapy in patients with hepatocellular carcinoma.

Condition being studied: Hepatocellular carcinomai s a common cancer worldwide and a importent cause of cancerrelated death. Although several therapies are used in the first-line treatment of hepatocellular carcinoma, the clinical outcome of patients are still not Satisfactory.

METHODS

Search strategy: A systematical search will be surched for associated studies published in the Pubmed, Embase and Cochrane Library. The search terms were as follows: "hepatocellular carcinoma/exp" and "randomized controlled trialail/exp" and ("vasculartropin/exp" or "anti-angiogenesis/exp" or "angiogenesis inhibitor/exp") and ("immune checkpoint inhibitor/exp" or "programmed cell death protein 1/exp" or "programmed cell death ligand protein 1/exp" or "cytotoxic T-lymphocyte-associated protein 4/exp") and "human/exp".

Participant or population: 18 years of age or older and had locally advanced metastatic or unresectable hepatocellular carcinoma (or both).

Intervention: Immune-checkpoint inhibitor and anti-VERF therapy.

Comparator: Sorafenib or lenvatinib.

Study designs to be included: Randomized clinical trials.

Eligibility criteria: The inclusion criteria were as follows:1) Patients who were diagnosed with HCC.2) Adults(18years old or older); 3) Studies reported with efficacy, including (overall survival (OS), progression-free survival (PFS) and objective response rate (ORR)) and associated AEs; 4) Randomized controlled trial studies;

Information sources: Datebase such as PubMed, the Cochrane Library, Embase, clinical trial website

Main outcome(s): Overall survival, pogress-free suirvival, objective response rate The total number of all treatment-related adverse events and the number of each specific treatment related adverse event.

Additional outcome(s): None.

Data management: The following data from eligible studies: National clinical trial (NCT) number, first author, treatment arms, control arms, the overall number of patients, publication year, enrollment criteria, characteristics of patients, outcomes, study methods and number of selected adverse events.

Quality assessment / Risk of bias analysis: The Cochrane Risk of Bias Tool was used to assess the quality of individual studies, in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. This tool considers selection bias, performance bias, attrition bias, detection bias, reporting bias, and other potential sources of bias. The overall risk of bias for each study was evaluated and rated as “low” when the risk of bias was low in all key domains; “unclear” when the risk of bias was low or unclear in all key domains; and “high” when the risk of bias was high in one or more key domains.

Strategy of data synthesis: The hazard ratios (HR) were represented with 95% confidence intervals (CI) for generic inverse variance outcomes, and risk ratios (RR)

were shown with 95% confidence intervals for outcomes. We adopted mean values for continuous outcomes. Statistical heterogeneity across trials or subgroups were tested by I2 testing.

Subgroup analysis: PD-L1 expression level, age, ECOG score, HBV infection.

Sensitivity analysis: Sensibility analysis was carried out to examine whether the was influenced by a single study by removing one study at a time.

Language: English.

Country(ies) involved: China.

Keywords: Combination therapy, Hepatocellular carcinoma,Immune checkpoint inhibitors, VEGFR targeted therapy, Efficacy, Safety.

Contributions of each author:

Author 1 - Huiyun Zhang drafted the manuscript and conducted the meta-analysis.
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