INPLASY PROTOCOL

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Conflicts of interest:
None declared.

A systematic review and network meta-analysis to evaluate efficacy and safety of immunotherapy in the first-line treatment of metastatic hepatocellular carcinoma

Zhang, L[1]; Zhang, H[2].

Review question / Objective: **Following the patient, intervention, comparison, outcome(PICO) framework, studies had to meet the following criteria: (I) patients with previously untreated metastatic hepatocellular carcinoma(mHCC); (II) studies compared the efficacy and safety of treatment strategies included anti-angiogenic agent with or without ICIs in the first-line setting for advanced or metastatic HCC; (III) reported outcomes included one or more of the following: OS, PFS, toxicity and ORR; (IV) studies were prospective randomized controlled trials (RCT s).**
Condition being studied: **We want to investigate safety and efficacy of anti-angiogenic agent combined with immune checkpoint inhibitoris in metastatic hepatocellular carcinoma (mHCC)patients, we performed a systematic review and meta-analysis to compare the clinical efficacy and immune-relate AEs of AA combined with ICI, and furthermore to optimize the application of advanced or metastatic HCC.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 August 2021 and was last updated on 24 August 2021 (registration number INPLASY202180090).

INTRODUCTION

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METHODS

Participant or population: Inclusion: studies were included if they met the following criteria: they were restricted to RCTs; treatment strategies included ICI with or without anti-angiogenic agent in the first line for advanced or metastatic HCC; Exclusion: Enrolled patients in trials had received previous systemic treatment.

Intervention: Studies compared the efficacy and safety of treatment strategies included anti-angiogenic agent with or without ICIs in the first-line setting for advanced or metastatic HCC.

Comparator: Immune checkpoint inhibitoris(atezolizumab, sintilimab, nivolumab), anti-VEGF antibody (bevacizumab, a bevacizumab biosimilar (IBI305))as a single agent or in combination.

Study designs to be included: Randomized controlled trials(RCTs) will be included.

Eligibility criteria: (1) prospective randomized controlled clinical studies were published in the form of full papers; (2) efficacy and safety data in the studies were extractable; (3) enrolled patients with unresectable locally advanced or metastatic hepatocellular carcinoma(HCC) and previously untreated; and (4) treatment strategies included anti-angiogenic agents with or without ICIs in the first line for advanced or metastatic HCC;(5)ICI includes anti-PD-1/PD-L1,anti-CTLA-4 inhibitors, or their any combination; (6) language limited to English or Chinese.

Information sources: We will search articles in three electronic database including PubMed, EMBASE and Cochrane Library.All the English and Chinese publications until 16 June 2021will be searched without any restriction of countries or article type.Reference list of all selected articles will independently screeed to identify additional studies left out in the initial search.In addition, we also manually reviewed meeting abstracts and presentations from ASCO, ESMO to identify the relevant studies.

Main outcome(s): Overall survival (OS) and progression-free survival (PFS)

Additional outcome(s): Overall Response Rate (ORR) and grade 3 and 5 adverse events (AEs) were secondary outcomes.

Data management: Types of study include previous studies (meta-analyses or network meta-analyses) which have assessed the relationship of these regimens with progression-free survival, overall survival overall Response Rate and adverse events in advanced or metastatic HCC. Extracted information will include: study population and participant demographics and baseline characteristics; details of the intervention and control conditions; outcomes and times of measurement; study methodology; outcomes and times of measurement; information for assessment of the risk of bias. We combine sufficiently similar studies in meta-analyses using random-effects models when there are at least four studies and fixed-effect models when fewer than four studies. Summary statistics for the primary endpoints were hazard ratio (HR) and odds ratios (OR). with their 95% confidence intervals (CIs). Data extraction was conducted according to the PRISMA statement. Two review authors will independently screen the results of the electronic searches, extracting data and assessed the risk of bias of the included studies. Any disagreement between them over the eligibility of particular studies will

be resolved through discussion with a third reviewer.

Quality assessment / Risk of bias analysis: Two investigators will independently evaluate the risk of bias and extract data from eligible trials. If only the standard deviations were missing, they will estimate from p values or with the mean standard deviation of the other included studies. Extracted data will be entered into standardized Excel (Microsoft Corp) file and are checked by another author. Any disagreements will be resolved by discussion and consensus. To assess the risk of bias of individual trials, we will apply the following components recommended by the Cochrane Collaboration: random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors (with blinding of at least the outcome assessors required for considering this parameter as low risk of bias); incomplete outcome data; selective outcome reporting; and other sources of bias.

Strategy of data synthesis: The hazard ratios (HRs) and their 95% confidence intervals (CIs) of survival data (PFS and OS) were extracted from the original literature and were calculated to evaluate the outcomes of therapeutic trials. The relative risk ratios (RRs) with 95% CIs were determined to evaluate the efficacy and safety of the treatment with both drugs. The heterogeneity of the studies in the meta-analysis was assessed using the I^2 metric and a χ^2 test. A random-effect model was used for the meta-analysis with large heterogeneity ($I^2 \geq 50\%$ and a χ^2 test with $P \leq 0.1$); otherwise, the fixed-effects model was used.

Subgroup analysis: This is a qualitative synthesis and while subgroup analyses may be undertaken it is not possible to specify the groups in advance.

Sensitivity analysis: Heterogeneity between studies was tested using the χ2 test and I2 statistics. P value for χ250% was considered statistically significant for heterogeneity, and the random-effects model was used to calculate statistical value in this situation. Otherwise, the fixed effect model was used.

Language: English.

Country(ies) involved: China.

Keywords: Metastatic hepatocellular carcinoma (mHCC); anti-angiogenic agent; immunotherapy; prognosis; meta-analysis.

Contributions of each author:
Author 1 - Zhang Li.
Author 2 - Zhang Hongzhen.