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Comprehensive evaluation of efficacy and safety in emerging first-line immunotherapies for advanced hepatocellular carcinoma: A systematic review and network meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2024110045

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 November 2024 and was last updated on 9 November 2024.

INTRODUCTION

Review question / Objective (1) Population (P): Adults (age ≥18 years) with unresectable advanced HCC. Advanced HCC was defined by the American Society of Clinical Oncology (ASCO) criteria as patients no longer suitable for surgical or liver-directed therapy, characterized by intrahepatic multifocal and/or infiltrative disease, vascular invasion, or extrahepatic spread. Alternatively, by the Barcelona criteria, presenting with vascular invasion or extrahepatic spread while still relatively fit (PS ≤ 2 at staging work-up) and having preserved liver function1.
(2) Intervention (I): Patients receiving any of the recommended first-line systemic treatments for advanced HCC, including: Atezolizumab plus Bevacizumab, Sorafenib, Lenvatinib and Durvalumab plus Tremelimumab2.
(3) Comparison (C): The choice of control group should be the standard treatment for each line of advanced HCC or existing therapies. For patients with recurrent refractory advanced HCC, where no standard treatment currently exists, if a placebo control is used, it should be combined with the best supportive care to ensure the benefit of the patients.
(4) Outcome (O): The primary outcome measure for this study is Overall Survival (OS), which evaluates the length of time from either the date of diagnosis or the start of treatment for a disease that patients diagnosed with the disease are still alive3. Secondary endpoints, such as Progression-Free Survival (PFS), Time to Progression (TTP), and Serious Advert Events (SAE), are considered optional and less critical compared to the primary endpoint of OS.
(5) Study Type (S): Phase III randomized controlled trials of first-line therapy in a palliative care setting, with open-label trials permitted.

Rationale Currently recommended first-line therapies have demonstrated survival benefit over

sorafenib in treating advanced hepatocellular carcinoma (HCC) in randomized controlled trials (RCT). However, the comparative safety and efficacy of these treatments remain unclear. This study investigated whether one treatment performed better than others in terms of safety and efficacy.

Condition being studied Hepatocellular carcinoma (HCC) remains one of the most common and lethal cancers worldwide, particularly in regions with a high prevalence of hepatitis B virus (HBV) infection, such as East Asia and Africa. Sorafenib, a tyrosine kinase inhibitor (TKI), was the first systemic treatment for advanced HCC [NEJM, 2008, 378-90], and remained the standard of care for almost fifteen years. In 2020, a major breakthrough occurred with the combination of atezolizumab and bevacizumab, which demonstrated superior overall survival compared to sorafenib [NEJM, 2020, 1894-1905]. This achievement marked a complete shift in first-line treatment. Recently, inspired by the success of atezolizumab plus bevacizumab, new therapeutic options including combinations of immunotherapies with VEGF inhibitors [Lancet, 2023, 1133-1146] and dual immunotherapeutic regimens [Ann Oncol, 2024, 537-548] have shown promising results, such as an extended median survival and enhanced safety profiles. However, given that each first-line regimen has distinct adverse effects and applicable patient populations, evaluating the efficacy and safety of emerging immunotherapies is critically important. The lack of direct head-to-head trials further complicates such comparisons in randomized controlled settings. Another key issue is how to comprehensively quantify both efficacy and safety, as more "effective" immunotherapies may carry the risk of life-threatening autoimmune hepatitis, and rapid tumor necrosis could also lead to edema, hemorrhage, or hepatic encephalopathy, further exacerbating patient mortality. Simply pursuing higher overall survival or response rates may not always be the most appropriate approach.

METHODS

Search strategy An extensive literature search of electronic databases, including PubMed, Web of Science, The Cochrane Library, and EMBASE, was conducted for relevant studies published from January 1, 2007, up to Sep 27, 2024. The reference lists of the retrieved studies and related reviews were manually searched to identify additional potentially relevant research. Additionally, ClinicalTrials.gov was manually queried to identify potential unpublished data.

Participant or population Population (P): Adults (age ≥18 years) with unresectable advanced HCC. Advanced HCC was defined by the American Society of Clinical Oncology (ASCO) criteria as patients no longer suitable for surgical or liver-directed therapy, characterized by intrahepatic multifocal and/or infiltrative disease, vascular invasion, or extrahepatic spread. Alternatively, by the Barcelona criteria, presenting with vascular invasion or extrahepatic spread while still relatively fit (PS ≤ 2 at staging work-up) and having preserved liver function1.

Intervention Intervention (I): Patients receiving any of the recommended first-line systemic treatments for advanced HCC, including: Atezolizumab plus Bevacizumab, Sorafenib, Lenvatinib , Durvalumab plus Tremelimumab and the other therapies.

Comparator Comparison (C): The choice of control group should be the standard treatment for each line of advanced HCC or existing therapies. For patients with recurrent refractory advanced HCC, where no standard treatment currently exists, if a placebo control is used, it should be combined with the best supportive care to ensure the benefit of the patients.

Study designs to be included Study Type (S): Phase III randomized controlled trials of first-line therapy in a palliative care setting, with open-label trials permitted.

Eligibility criteria Inclusion Criteria
(1) Population (P): Adults (age ≥18 years) with unresectable advanced HCC. Advanced HCC was defined by the American Society of Clinical Oncology (ASCO) criteria as patients no longer suitable for surgical or liver-directed therapy, characterized by intrahepatic multifocal and/or infiltrative disease, vascular invasion, or extrahepatic spread. Alternatively, by the Barcelona criteria, presenting with vascular invasion or extrahepatic spread while still relatively fit (PS ≤ 2 at staging work-up) and having preserved liver function1.
(2) Intervention (I): Patients receiving any of the recommended first-line systemic treatments for advanced HCC, including: Atezolizumab plus Bevacizumab, Sorafenib, Lenvatinib and Durvalumab plus Tremelimumab2.
(3) Comparison (C): The choice of control group should be the standard treatment for each line of advanced HCC or existing therapies. For patients with recurrent refractory advanced HCC, where no standard treatment currently exists, if a placebo control is used, it should be combined with the

best supportive care to ensure the benefit of the patients.
(4) Outcome (O): The primary outcome measure for this study is Overall Survival (OS), which evaluates the length of time from either the date of diagnosis or the start of treatment for a disease that patients diagnosed with the disease are still alive3. Secondary endpoints, such as Progression-Free Survival (PFS), Time to Progression (TTP), and Serious Advert Events (SAE), are considered optional and less critical compared to the primary endpoint of OS.
(5) Study Type (S): Phase III randomized controlled trials of first-line therapy in a palliative care setting, with open-label trials permitted.
Exclusion criteria
(1) Non-research articles, including meta-analyses, editorials, commentaries, letters, new articles, case reports, and narrative reviews;
(2) Studies not published in English;
(3) Studies with missing baseline date, or those that did not report the primary endpoint of Overall Survival (OS);
(4) Studies with PICOS designs that differ significantly from other trials;
(5) Non-phase III randomized controlled trials (RCTs);
(6) Studies involving patients who underwent liver resection, transarterial chemoembolization (TACE), or other localized treatments prior to systemic therapy;
(7) Studies where more than half of the patients have poor baseline characteristics, such as an ECOG performance status ≥2 or a Child-Pugh C score;
(8) Studies that do not include a sorafenib treatment arm as part of the design;
(9) Studies exploring treatments not recommended as first-line therapy by ASCO advanced HCC guideline;
(10) Studies with High Risk of bias (Rob2) and Very Low GRADE evidence ratings;
(11) Studies that do not provide time-to-event data necessary for calculating hazard ratios (HR).

Information sources An extensive literature search of electronic databases, including PubMed, Web of Science, The Cochrane Library, and EMBASE, was conducted for relevant studies published from January 1, 2007, up to June 27, 2024. The reference lists of the retrieved studies and related reviews were manually searched to identify additional potentially relevant research. Additionally, ClinicalTrials.gov was manually queried to identify potential unpublished data.

Main outcome(s) OS, PFS, SAEs.

Quality assessment / Risk of bias analysis The quality of the included trials was independently assessed by two reviewers (Li H and Lai J) with the Cochrane Risk- of- Bias assessment tool version 2, (RO2) for randomized trials and the certainty of evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Strategy of data synthesis Statistical analyses were conducted in R version 4.3.3. We compared the efficacy endpoint, such as OS and PFS by using hazard ratios (HR). Safety endpoints were the rate of Serious Adverse Events (SAE), and compared by using odds ratios (OR). The 95% confidence intervals (CI) for all metrics were reported, and all P-values were two-sided, with $P < 0.05$ considered statistically significant. The calculation of P-value is based on Wald test16.
Network meta-analysis was performed with the frequentist model with a graph-theoretical approach implemented in the R package netmeta17. The weight matrix was calculated based on the inverse-variance weighting method and the estimates of indirect effects between different treatment regimens were obtained based on the Moore-Penrose pseudoinverse method18. We initially conducted the network meta-analysis using the fixed-effects model, calculating the Q statistic and I^2 (with $I^2 > 50\%$ or $P < 0.1$ indicating heterogeneity)8.
Our network graph did not contain loops, meaning the absence of direct head-to-head trials between these first-line therapies in a randomized environment. Therefore, it was impossible to split the network to assess heterogeneity19, and checking for inconsistency was not feasible. On the other hand, a method of multi-criteria decision analysis (MCDA)20, is used for indicating specific treatment we finally determined, by integrating three elements of OS, PFS, and SAE to construct a weight function about the ranking effect value Q.
Potential publication bias was assessed by checking the outcome of Egger's test.

Subgroup analysis Based on the patient' baseline characteristics, etiologies, and biochemical indicators, separate analyses were conducted across eight subgroups (appendix pp 24-28). In most subgroups, the therapies were categorized into three tiers: the placebo group, the baseline group (including sorafenib and lenvatinib), and the new first-line group. Each tier demonstrated significant improvements in OS over the previous one, with no significant differences observed between therapies within the same tier. Among the new first-line therapies, doublet therapy with sintilimab pius bevacizumab performed best,

particularly in the HBV subgroup, where it showed a clear advantage over atezolizumab plus bevacizumab and camrelizumab plus apatinib, indicating its greater potential for use in specific populations.

Sensitivity analysis Due to the low heterogeneity observed in the included studies, sensitivity analysis was not conducted.

Language restriction No.

Country(ies) involved China (Sun Yat-sen University).

Other relevant information No

Keywords advanced hepatocellular carcinoma; immunotherapy; camrelizumab plus apatinib; sintilimab plus bevacizumab; nivolumab plus ipilimumab.

Contributions of each author

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