

INPLASY PROTOCOL

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None declared.

Effectiveness and Safety of Locoregional Combined with Systemic Therapies for Unresectable Hepatocellular Carcinoma: a Bayesian Network Meta-analysis

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Review question / Objective: This study aimed to assess the clinical efficacy and safety of locoregional therapy in combination with systemic therapy for unresectable hepatocellular carcinoma by a Bayesian Network Meta-analysis. **Participants:** The target patients will be adults with hepatocellular carcinoma who are ineligible for surgery initially because of hard to achieve R0 resection according to "Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China" (2022 Edition)" or the criteria of Barcelona. **Interventions:** local therapy (contain criteria: any local therapy received as Transarterial chemoembolization (e.g., Conventional-Transarterial chemoembolization (c-TACE), Drug-eluting beads-Transarterial chemoembolization (DEB-TACE), etc.), or Hepatic arterial infusion chemotherapy (HAIC), or radiotherapy or selective internal radiation therapy (SIRT)) combine with systemic therapy (inclusion criteria: any systemic therapy received anti-VEGF/EGFR agents, or Tyrosine Kinase Inhibitors, or Immuno-Checkpoint Inhibitors, or chemotherapies, or their combination). **Comparisons:** 1. Monotherapy of local therapy, or monotherapy of systemic therapy, or placebo will be the controls; 2. Any relevant comparator including different types of local therapy plus different types of systemic therapy. **Outcomes:** Main outcomes: Objective response rate (ORR) By RECIST 1.1/mRECIST; Adverse Events(AEs); Secondary outcome: Overall survival (OS); Conversion resection rate(CRR); Disease progression free time (PFS) By RECIST 1.1/mRECIST.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 April 2022 and was last updated on 01 April 2022 (registration number INPLASY202240009).

INTRODUCTION

Review question / Objective: This study aimed to assess the clinical efficacy and

safety of locoregional therapy in combination with systemic therapy for unresectable hepatocellular carcinoma by a Bayesian Network Meta-analysis.

Participants: The target patients will be adults with hepatocellular carcinoma who are ineligible for surgery initially because of hard to achieve R0 resection according to "Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China" (2022 Edition)" or the criteria of Barcelona. **Interventions:** local therapy (contain criteria: any local therapy received as Transarterial chemoembolization (e.g., Conventional-Transarterial chemoembolization (c-TACE), Drug-eluting beads-Transarterial chemoembolization (DEB-TACE), etc.), or Hepatic arterial infusion chemotherapy (HAIC), or radiotherapy or selective internal radiation therapy (SIRT)) combine with systemic therapy (inclusion criteria: any systemic therapy received anti-VEGF/EGFR agents, or Tyrosine Kinase Inhibitors, or Immuno-Checkpoint Inhibitors, or chemotherapies, or their combination). **Comparisons:** 1. Monotherapy of local therapy, or monotherapy of systemic therapy, or placebo will be the controls; 2. Any relevant comparator including different types of local therapy plus different types of systemic therapy. **Outcomes:** Main outcomes: Objective response rate (ORR) By RECIST 1.1/mRECIST; Adverse Events(AEs); Secondary outcome: Overall survival (OS); Conversion resection rate(CRR); Disease progression free time (PFS) By RECIST 1.1/mRECIST.

Condition being studied: Hepatocellular carcinoma (HCC), the most common type in primary liver cancer, is one of the leading causes of human cancer-related deaths, and carries significant burden for individual and society. As most patients with HCC are diagnosed at an intermediate- to advanced-stage, the opportunity for radical surgery is lost. In recent years, the systemic treatment and comprehensive treatment have made a substantial-advances which means an increasing numbers of patients with unresectable hepatocellular carcinoma expected to have a better survival benefits from radical surgery after successful conversion therapy. However, we still lacking higher

level evidences to support the different treatment options.

METHODS

Participant or population: The target patients will be adults with hepatocellular carcinoma who are ineligible for surgery initially because of hard to achieve R0 resection according to "Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China" (2022 Edition)" or the criteria of Barcelona.

Intervention: Local therapy (contain criteria: any local therapy received as Transarterial chemoembolization (e.g., Conventional-Transarterial chemoembolization (c-TACE), Drug-eluting beads-Transarterial chemoembolization (DEB-TACE), etc.), or Hepatic arterial infusion chemotherapy (HAIC), or radiotherapy or selective internal radiation therapy (SIRT)) combine with systemic therapy (inclusion criteria: any systemic therapy received anti-VEGF/EGFR agents, or Tyrosine Kinase Inhibitors, or Immuno-Checkpoint Inhibitors, or chemotherapies, or their combination).

Comparator: 1. Monotherapy of local therapy, or monotherapy of systemic therapy, or placebo will be the controls; 2. Any relevant comparator including different types of local therapy plus different types of systemic therapy.

Study designs to be included: (1)Randomised controlled trials (RCTs); (2)non-randomised comparative trials for specific interventions where RCTs evidence has been evaluated as insufficient or of poor quality.

Eligibility criteria: (1)Patients who were firstly diagnosed unresectable hepatocellular carcinoma according to CSCO or NCCN guidelines and had not received any prior treatment;(2) Reported at least one clinical outcome of interest including ORR, AEs, OS, CRR and so on.

Information sources: At a minimum, we will systematically search the following

databases: PubMed, Embase, Web of Science, Cochrane Library, Scopus, Ovid, ProQuest, clinical trial website, CNKI, WANFANG, VIP, CBM.

Main outcome(s): Objective response rate (ORR) By RECIST 1.1/mRECIST; Adverse Events(AEs).

Additional outcome(s): Overall survival (OS); Conversion resection rate(CRR); Disease progression free time (PFS) By RECIST 1.1/mRECIST.

Quality assessment / Risk of bias analysis: The final included studies will be assessed by the Cochrane Risk of Bias Tool. We will record the quality of the assessed studies and will evaluate the impact of their quality on the results of the analysis.

Strategy of data synthesis: First of all, all analysis of this study will be based on the R 4.1.3 primarily. Statistical heterogeneity of all included literatures will be estimate by I². If I²>50%, the randomized-effects model will be used or depending on the specific source of heterogeneity to perform subgroup analysis or not; If I²<50%, the fixed-effects model will be adopted. The network meta-analysis will be based on Bayesian model with Markov Chain Monte Carlo methods. Moreover, the sensitivity analysis and other accuracy-related assessment of model results will be carried out.

Subgroup analysis: Relevant subgroup analyses (e. g. combined portal thrombosis or not, study location, Child-Pugh A/B/C, number of lesions etc.) will be performed if conditions permit.

Sensitivity analysis: After randomly excluding any of the papers, the results are considered to pass the sensitivity analysis if they are not significantly different from those without exclusion

Country(ies) involved: China.

Keywords: hepatocellular carcinoma; conversion therapy; local therapy; systemic therapy.

Contributions of each author:

Author 1 - Chen Xinnian.