INPLASY PROTOCOL

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None declared.

Risk of Pneumonitis of Hepatocellular Carcinoma Patients with the use of Immune Checkpoint Inhibitors: A systematic Review and Network Meta-analysis

Deng, H[1]; Li, Y[2]; Jiang, H[3]; Jiang, X[4]; Gou, Y[5].

Review question / Objective: **The aim is to explore the risk of pneumonitis in patients with hepatocellular carcinoma after receiving immune checkpoint inhibitors.**
Condition being studied: **The pneumonitis associated with immune checkpoint inhibitors (ICIs) is a rare but high lethal disease. Recent years, more and more ICIs have been approved for hepatocellular carcinoma patients, whereas we know less about the risk of immune-associated pneumonitis in HCC patients post-administrating with ICIs.**
Information sources: **Two independent reviewers searched related studies comprehensively and systematically through four English electronic databases (Web of Science, PubMed, Cochrane Library, and Embase) using the main MeSH terms. Manual research was also performed.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 June 2022 and was last updated on 12 June 2022 (registration number INPLASY202260051).

INTRODUCTION

Review question / Objective: **The aim is to explore the risk of pneumonitis in patients with hepatocellular carcinoma after receiving immune checkpoint inhibitors.**

Condition being studied: **The pneumonitis associated with immune checkpoint inhibitors (ICIs) is a rare but high lethal disease. Recent years, more and more ICIs have been approved for hepatocellular carcinoma patients, whereas we know less about the risk of immune-associated**

pneumonitis in HCC patients post-administrating with ICIs.

METHODS

Participant or population: Patients with hepatocellular carcinoma.

Intervention: HCC treatments were treated with multiple ICIs, including ipilimumab, tremelimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, toripalimab, camrelizumab, and sintilimab.

Comparator: Placebo, chemotherapeutic drugs, targeted drugs, or immune checkpoint inhibitors.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: The inclusion criteria were as follows: (i) studies identified as only randomized controlled trials (RCTs) in phase 2/3/4 that published in English were included; (ii) The enrolled patients in RCTs were rigorously diagnosed with HCC, and were confirmed pathologically, histologically, or radiographically, regardless of stage (early, intermediate, and advanced or terminal) and severity (metastatic or non-metastatic) ; (iii) patients with HCC were treated with at least one ICI, and ICI therapies were assigned as experimental arms within RCT; (iv) studies reporting the events or incidence of all grades (1-5) and grade 3-5 of immune-associated pneumonitis (IAP) were eligible. The exclusion criteria were as follows: (i) studies with insufficient data or ongoing trials did not meet the inclusion criteria; (ii) RCT in phase 1 and trials without a control arm (single arm) were excluded; (iii) system reviews, meta-analysis, animal studies, case reports, conferences, letters, comments, and editorials.

Information sources: Two independent reviewers searched related studies comprehensively and systematically through four English electronic databases (Web of Science, PubMed, Cochrane Library, and Embase) using the main MeSH terms. Manual research was also performed.

Main outcome(s): Risk of immune-associated pneumonitis (IAP).

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: The quality of each eligible study was judged using the Cochrane risk bias assessment tools. Estimate of the certainty of evidence was performed using GRADE method (Grading of Recommendation Assessment, Development, and Evaluation).

Strategy of data synthesis: First, we conducted traditional pairwise meta-analysis to directly compare interventions with observation. Heterogeneity of the included studies was examined using the X2 test and depicted as I2. If $P > 0.1$ and $I2 < 50\%$, the fixed-effect model was applied for data analysis. Else, a random-effect model was used. Secondly, network meta plot and publication bias were performed using, frequentist-based Stata/SE (ver. 15.1). Thirdly, the network meta-analysis was performed using R statistical software version 4.2.0 (R Project for Statistical Computing) with package “gemtc” (version 1.0.1, R foundation).

Subgroup analysis: None.

Sensitivity analysis: None.

Country(ies) involved: China.

Keywords: immune-associated pneumonitis, hepatocellular carcinoma, immune checkpoint inhibitors, network meta-analysis, programmed death protein 1.

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