ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 December 15; 16(12): 4532-4781

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.5; 5-year JIF: 2.8; JIF Rank: 72/143 in gastroenterology and hepatology; JIF Quartile: Q3; and 5-year JIF Quartile: Q2. The *WJGO*'s CiteScore for 2023 is 4.2 and Scopus CiteScore rank 2023: Gastroenterology is 80/167; Oncology is 196/404.

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NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
December 15, 2024

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World J Gastrointest Oncol 2024 December 15; 16(12): 4766-4769

DOI: 10.4251/wjgo.v16.i12.4766

ISSN 1948-5204 (online)

LETTER TO THE EDITOR

Current efficacy of hepatic arterial infusion chemotherapy in hepatocellular carcinoma

Douglas Dias E Silva, Mitesh Borad, Pedro Luiz Serrano Uson Junior

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Xi Z

Received: July 21, 2024
Revised: August 28, 2024
Accepted: October 12, 2024
Published online: December 15, 2024
Processing time: 113 Days and 14.9 Hours

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Abstract

Newer systemic therapies for hepatocellular carcinoma (HCC) have led to growing interest in combining hepatic arterial infusion chemotherapy (HAIC) with systemic treatments. To evaluate the effectiveness and safety of HAIC and combination therapies in treating advanced HCC, a network meta-analysis was conducted by Zhou *et al*. The study included data from 44 articles. HAIC was superior in overall survival (OS), progression-free survival (PFS), and response rates compared to transarterial chemoembolization and sorafenib. Moreover, combinations of HAIC with other treatments and single agents (*e.g.*, lenvatinib, ablation, anti-programmed cell death 1 therapy, radiotherapy) provided better OS and PFS outcomes than HAIC alone. In this editorial, we will discuss the study findings, the strengths and weaknesses of the metanalysis, and future advances in the field of HAIC for advanced HCC.

Key Words: Hepatic arterial infusion; Chemotherapy; Hepatocellular carcinoma; Liver cancer; Survival

Core Tip: This meta-analysis provides a valuable and comprehensive evaluation of hepatic arterial infusion chemotherapy (HAIC) and its combination therapies for advanced hepatocellular carcinoma. Compared to other treatments including transarterial chemoembolization, HAIC showed favorable outcomes including response rate and survival. Furthermore, based on the findings, combination of HAIC with antiangiogenics and even immune checkpoint inhibitors seems to improve efficacy when compared to HAIC alone.

Citation: Dias E Silva D, Borad M, Uson Junior PLS. Current efficacy of hepatic arterial infusion chemotherapy in hepatocellular carcinoma. *World J Gastrointest Oncol* 2024; 16(12): 4766-4769
URL: https://www.wjgnet.com/1948-5204/full/v16/i12/4766.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i12.4766

INTRODUCTION

Liver cancer remains a global health challenge, with an estimated incidence of > 1 million cases by 2025[1]. Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer, accounting for more than 90% of cases[2,3]. Recent advances in systemic therapies with the inclusion of targeted therapy and immunotherapy have led to changes in many guidelines regarding systemic therapy for advanced disease[4]. Despite these advancements, outcomes related to advanced disease are still poor[5,6]. Another option for the treatment of selected cases of advanced disease is hepatic arterial infusion chemotherapy (HAIC) alone or in combination with other strategies[7]. This therapy is recommended for Japanese guidelines based on studies of this population with promising results, especially for the treatment for advanced HCC with portal vein tumor thrombus[6]. Additionally, there are data showing that HAIC results in fewer adverse events compared to other intra-hepatic therapies, such as transarterial chemoembolization (TACE)[7,8]. Due to the lack of adequate phase 3 randomized controlled trials, there is not enough evidence to confirm that patients with HCC can gain significant benefits from HAIC. Consequently, Zhou *et al*[9] conducted a meta-analysis to provide insight into evidence-based medicine for the use of HAIC.

THE META-ANALYSIS

Zhou *et al*[9] carried out a network meta-analysis examining the effectiveness and safety of HAIC and its combination treatments for advanced HCC. This analysis included data from nine randomized controlled trials and thirty-five cohort studies[9]. Key outcomes assessed included overall survival (OS), progression-free survival (PFS), tumor response, and adverse events, with hazard ratios and odds ratios calculated for comparison. The results indicated that HAIC significantly outperformed Sorafenib and TACE in terms of efficacy and safety. Furthermore, HAIC in combination with therapies such as lenvatinib, ablation, anti-programmed cell death 1 (anti-PD-1), and radiotherapy resulted in improved OS in addition to PFS related to HAIC without association with other toxicities. Moreover, combination therapies such as HAIC with TACE and S-1, HAIC with lenvatinib, and HAIC with anti-PD-1 showed higher partial response rates and objective response rates. Overall, HAIC combined with anti-PD-1, TACE + S-1, and TACE achieved superior complete response and disease control rates compared to HAIC alone. The main results presented by the meta-analysis are described in Table 1.

DISCUSSION

The inclusion of nine randomized controlled trials and 35 cohort studies provides broad and robust data, enhancing the reliability of the findings. Additionally, the study evaluates multiple critical outcomes such as OS, PFS, tumor response, and adverse events, offering a wide overview of the efficacy and safety of HAIC and its combinations. The analysis of HAIC in combination with other treatments (*e.g.*, lenvatinib, programmed cell death 1, radiotherapy) provides valuable insights into potential synergistic effects and paves the way for future trials considering safety data of those regimens. However, the inclusion of both randomized controlled trials and cohort studies, despite increasing the number of patients included in the meta-analysis, could introduce significant heterogeneity in study designs, patient populations, and treatment protocols, potentially impacting the consistency of the results. The findings might not be universally applicable, especially if the included studies predominantly involve certain demographics or regions. Moreover, the studies included do not represent the current landscape of HCC treatment, notably related to the control group, which does not include combined immunotherapy regimens as recommended by current guidelines based on phase III studies compared to tyrosine kinase inhibitors.

When evaluating the quality assessment of trials included, some selection bias inherent to the metanalysis was identified. For example, most randomized controlled trials were not blinded. This could be very important when evaluating endpoints such as response rate and PFS. Moreover, most studies also had publication bias, easily identified in the funnel plots of responses and adverse events. There are also other limitations important to discuss. Variations in

Table 1 Summary of meta-analysis key findings

Outcome	Number of studies	Main results (HR/OR, 95%CI)	Conclusions and ranking (*P* value)
OS	41 (9 RCTs, 32 cohorts)	HAIC + Lenv + A: HR = 0.12 (0.03-0.57) HAIC + A: HR = 0.21 (0.07-0.67) HAIC + Lenv: HR = 0.29 (0.11-0.74) HAIC + Sora: HR = 0.52 (0.33-0.81)	HAIC + Lenv + A showed the best OS (*P* value: 0.94), followed by HAIC + A (*P* value: 0.85)
PFS	30 (9 RCTs, 21 cohorts)	HAIC + A: HR = 0.25 (0.08-0.77) HAIC + TACE: HR = 0.32 (0.14-0.75) HAIC: HR = 0.51 (0.33-0.78)	HAIC + A had the most favorable PFS outcomes (*P* value: 0.79)
CR	35 (8 RCTs, 27 cohorts)	HAIC + Sora: OR = 7.62 (2.55-22.77) HAIC: OR = 2.86 (1.37-5.98)	HAIC + Sora showed the best CR outcomes (*P* value: 0.86)
PR	35 (8 RCTs, 27 cohorts)	HAIC + TACE + S-1: OR = 13.29 (3.63-48.61) HAIC + Lenv: OR = 8.37 (4.32-16.23)	HAIC + TACE + S-1 had the best PR outcomes (*P* value: 0.90), followed by HAIC + Lenv (*P* value: 0.79)
ORR	35 (8 RCTs, 27 cohorts)	HAIC + TACE + S-1: OR = 17.88 (2.22-143.80) HAIC + Lenv: OR = 13.92 (3.25-59.60)	HAIC + TACE + S-1 showed the best ORR outcomes (*P* value: 0.79)
DCR	35 (8 RCTs, 27 cohorts)	HAIC + TACE + S-1: OR = 8.52 (1.56-46.49) HAIC + PD-1: OR = 7.26 (1.97-26.84)	HAIC + TACE + S-1 had the best DCR outcomes (*P* value: 0.88)
Any grade AEs	12 (4 RCTs, 12 cohorts)	HAIC: OR = 0.48 (0.25-0.92) HAIC + Lenv: OR = 0.19 (0.05-0.72)	HAIC showed the lowest incidence of any grade AEs (*P* value: 0.85)
Grade 3-4 AEs	16 (5 RCTs, 11 cohorts)	HAIC + Sora: OR = 0.26 (0.07-0.97) HAIC + Lenv: OR = 0.65 (0.12-3.43)	HAIC demonstrated lower trends of grade 3-4 AEs than HAIC + Sora and TACE

A: Anti-angiogenic agent; AEs: Adverse events; CR: Complete response; DCR: Disease control rate; HAIC: Hepatic arterial infusion chemotherapy; HR: Hazard ratio; Lenv: Lenvatinib; OR: Odds ratio; ORR: Objective response rate; OS: Overall survival; PD-1: Programmed death 1; PFS: Progression-free survival; PR: Partial response; RCT: Randomized controlled trial; S-1: Oral fluoropyrimidine (composite preparation of 5-FU prodrug); Sora: Sorafenib; TACE: Transarterial chemoembolization.

HAIC drugs (*i.e.* cisplatin or oxaliplatin), dosing regimens and drug dosages in the studies included were not considered. This could result in varying efficacy and safety profiles. The inclusion of anti-PD-1 without specifying the drug and the exclusion of some relevant studies due to their small number could also impact the interpretation of the findings and exacerbate the publication bias. Finally, the inability to conduct a subgroup analysis for portal vein tumor thrombus despite its recommendation in Japanese guidelines limits the analysis's applicability to this specific condition.

It is important to note that standard first-line treatment for advanced HCC is currently based on immunotherapy for eligible patients[10]. Combinations like durvalumab and tremelimumab, atezolizumab and bevacizumab, sintilimab and IBI305 and nivolumab plus ipilimumab are superior to tyrosine kinase inhibitors for upfront treatment in most patients, independently of etiology of cirrhosis or disease burden[10-13]. Furthermore, these combinations associated with TACE have proven to be a very attractive and potent strategy of treatment for patients with intermediate stage (BCLC B)[14]. In the EMERALD1 trial, a combination of TACE with durvalumab and bevacizumab led to an impressive objective response rate of 43%[14]. In conclusion, although HAIC is an important treatment option, it would need to be compared to these regimens to be considered a standard upfront treatment option for most patients with advanced HCC.

CONCLUSION

This meta-analysis provides a valuable and comprehensive evaluation of HAIC and its combination therapies for advanced HCC, highlighting their potential benefits in specific clinical situations, conducted by specialized centers. Significant unmet needs in HCC management could be addressed through the discovery of new therapies and their combinations, particularly for advanced-stage disease. This includes biomarkers for therapy stratification, patient-tailored strategies targeting driver mutations and/or activating signaling cascades, and validated quality-of-life measurements. Based on the findings of this meta-analysis, HAIC should be investigated with more potent and modern regimens to improve outcomes for this challenging disease.

FOOTNOTES

Author contributions: Dias e Silva D, Borad M, and Uson Junior PLS wrote and revised the article, reviewed the literature, and approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts-of-interest.

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S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Chen YX

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