Sorafenib is more effective in the treatment of TACE-refractory hepatocellular carcinoma than hepatic arterial infusion chemotherapy: a meta-analysis

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Research

Keywords: Sorafenib, Hepatic Arterial Infusion Chemotherapy, TACE-refractory, Hepatocellular Carcinoma, Meta-analysis

Posted Date: May 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-28648/v1>

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Abstract

Background: Currently, several studies have compared the efficacy of hepatic arterial infusion chemotherapy (HAIC) and sorafenib in the treatment of TACE-refractory hepatocellular carcinoma (HCC), but the conclusion is inconsistent. The purpose of this meta-analysis was to compare the effectiveness of sorafenib and HAIC in patients with TACE-refractory HCC.

Methods Multi-databases were searched to identify relevant studies published from inception to March 2020. The quality evaluation and data extraction were carried out for the selected articles meeting the inclusion and exclusion criteria. The data was analyzed using STATA16.

Results Five studies with 583 patients were included. Although the objective response rate in the HAIC group was significantly higher than that in the sorafenib group (RR = 3.08, 95%CI [1.38, 6.87], $p=0.006$), the overall survival (OS) was significantly shorter than that in the patients receiving sorafenib treatment (HR = 1.69, 95% CI [1.09, 2.62], $p=0.018$). Progression-free survival (HR = 1.21, 95% CI [0.76, 1.92], $p=0.426$) and disease control rate (RR = 0.94, 95% CI [0.60, 1.48], $p=0.798$) were not significantly different between the two groups.

Conclusion Compared with HAIC, patients with TACE- refractory HCC in the sorafenib group can obtain significantly longer OS. Sorafenib may be more suitable for the treatment of patients with TACE-refractory HCC. High-quality evidence is needed.

Background

Hepatocellular carcinoma (HCC) is one of the most common primary liver cancer, ranked sixth in the most common tumor, is the third leading cause of death of cancer[1]. Hepatectomy can significantly increase the survival rate of patients with HCC, which is the primary treatment of HCC [2, 3]. However, the postoperative recurrence rate is high, and the long-term prognosis of patients with HCC resection is unsatisfactory [4].

Transcatheter arterial chemoembolization (TACE) is often used to treat the postoperative recurrence of HCC. It is currently recognized as one of the most commonly used methods for non-surgical treatment of HCC[5-11]. However, after repeated TACE, some patients have no apparent response to TACE or disease progression and enter a TACE-refractory state. The concept of TACE refractoriness was proposed in the Liver Cancer Study Group of Japan (LCSGJ) and the clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) [12, 13]. And hepatic arterial infusion chemotherapy (HAIC) or sorafenib were both recommended for TACE-refractory HCC patients according to JSH-LCSGJ Consensus Criteria [14].

Sorafenib, a multi-kinase inhibitor, demonstrated a prolonged overall survival and time-to-progression in patients with advanced HCC[15, 16], also showing an excellent therapeutic effect in the treatment of TACE-refractory HCC patients [17, 18]. HAIC was recommended for the treatment of advanced liver cancer in Japan and showed good efficacy in the treatment of TACE-refractory HCC patients [19]. Although HAIC or sorafenib were both recommended for the TACE-refractory HCC [14], the knowledge as to which regimen is better or which one carries the more prolonged overall survival (OS) lacks the support of evidence-based medicine. Currently, several studies have compared the efficacy of HAIC and sorafenib in the treatment of TACE-refractory HCC, but but the conclusion is inconsistent[20, 21]. To compare the clinical effectiveness of HAIC with sorafenib in the treatment of TACE-refractory HCC, we conducted this study.

Methods

This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0.) and reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Inclusion and Exclusion Criteria

The subjects included in the study were TACE-refractory HCC adult patients who had not received HAIC or sorafenib treatment before. The interventions were HAIC or oral sorafenib alone, and the efficacy of the two treatments was compared. All included studies were required to report at least one outcome event: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Studies that cannot extract complete data, such as abstracts and letters, are excluded; Studies with fewer than 20 cases were excluded. No language restrictions were applied.

Literature search and study selection

Pubmed, *Web of Science*, *Cochrane library* and *Embase* were searched to identify relevant studies published from inception to March, 2020. Literature search and selection were independently conducted by 2 researchers (S.W., and L.P.). We resolved disagreements by discussing. The retrieval strategy in *Pubmed* was as follows: ((((((nexavar [Title/Abstract]) OR sorafenib [Title/Abstract]) AND ((((((TACE) OR (((transarterial [Title/Abstract]) OR transcatheter [Title/Abstract]) AND ((chemoembolization [Title/Abstract]) OR chemoembolization [Title/Abstract]) AND (((hepatic) AND arterial) AND Chemotherapy)))))))).

Data extraction and bias risk assessment

Two researchers independently conducted data extraction and bias risk assessment and resolved disagreements by discussing. Extract baseline characteristics, OS, PFS, ORR, and DCR. We assessed the risk of bias of included RCTs according to the Cochrane Collaboration's tool for assessing risk of bias. Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of non-randomized controlled trials. We quantified the quality of the research on a scale of 0-9. When the total score was >6, we considered the study to be of high quality. We use funnel plots to assess publication bias.

Data analysis

The data were analyzed using STATA 16. For OS and PFS, Hazard Ratio (HR) and 95% Confidence Interval (CI) were used for statistical analysis. For the study of unreported HR and its 95% CI, we extracted survival data from survival curves and then calculated HR and 95% CI using the appropriate statistical method and calculation table compiled by Matthew Sydes and Jayne Tierney [22]. For dichotomous variables, we used Risk Ratio (RR) and 95% CI for statistical analysis. The Q test and I^2 evaluated heterogeneity. When $I^2 > 50\%$ or $P < 0.1$, considering the heterogeneity between studies, the random effect model was used for meta-analysis. When the number of included studies was >10, meta-regression and subgroup analysis were used to detect the source of heterogeneity. Otherwise, use the fixed effects model. When the p-value was less than 0.05, we considered the results to be statistically significant. We performed sensitivity analyses to determine the stability of the results.

Results

Eligible studies

A total of 260 records were retrieved. Five articles [20, 23-26] and 583 patients were involved in the meta-analysis. The detail of the literature selection process was presented in Figure 1. All the included were retrospective studies, and the baseline characteristic of studies was shown in Table 1. TACE-refractory HCC was diagnosed according to the guidelines of JSH and LCSGJ [12, 13].

Risk of bias assessment

We used NOS tools to assess the quality of the included studies and presented the results of the bias risk assessment in Table 2.

OS

Four included articles [20, 23-25] reported the HR and 95%CI of OS in the HAIC group compared with the sorafenib group. The HR and 95%CI of 1 article were obtained from the survival curve [26]. The results of the meta-analysis showed that the sorafenib group had longer survival time than the HAIC group (HR = 1.69, 95% CI [1.09, 2.62], $p=0.018$, Figure 2A).

PFS

Two included articles [20, 24] reported the PFS of HR and 95%CI of patients in the HAIC group compared with the sorafenib group. The HR and 95%CI of 1 article [23] were extracted from the survival curve. The results of the meta-analysis showed no significant difference in PFS between the two groups (HR = 1.21, 95%CI [0.76, 1.92], $p=0.426$, Figure 2B).

ORR

Five studies reported the ORR. The results of the meta-analysis showed that the ORR of patients in the HAIC group was significantly higher than that in the sorafenib group (RR = 3.08, 95%CI [1.38, 6.87], $p=0.006$, Figure 3A).

DCR

DCR was reported in all five included articles. The results of the meta-analysis showed that there was no significant difference in the DCR between the two groups (RR = 0.94, 95%CI [0.60, 1.48], $p=0.798$, Figure 3B).

Sensitive analysis

We performed a sensitivity analysis for the meta-analysis results of OS. The pooled overall effect did not change significantly after the studies were excluded one by one (Figure 4A). The sensitivity analysis results indicated that the results of the meta-analysis were stable.

Assessment of publication bias

We used a funnel plot to evaluate the publication bias of the included studies, and the two sides of the funnel plot were symmetrical (Figure 4B). The p values of Begg's test and Egger's test were both > 0.05 , indicating that there was no obvious publication bias in the study.

Discussion

Compared with sorafenib, HAIC shows a better therapeutic effect and a lower incidence of adverse events (AEs) in the treatment of advanced or unresectable HCC [27-29]. HAIC has been widely used in Japan [12]. For TACE-refractory HCC, HAIC presents a satisfactory therapeutic effect[19, 20]. Sorafenib, as the first-line drug for advanced HCC, also has good efficacy in the treatment of TACE-refractory HCC[24, 30, 31]. As far as we know, this study is the first systematic review and meta-analysis to evaluate the efficacy of HAIC and sorafenib in the treatment of TACE-refractory HCC.

Through systematic literature retrieval, a total of 5 articles were included in this study. Different from the conclusion of previous systematic reviews [27-29], the study showed that sorafenib could prolong the overall survival of patients with TACE-refractory HCC compared with HAIC (HR = 1.69, 95% CI [1.09, 2.62], $p=0.018$). Although the ORR of the HAIC group was significantly higher than that of the sorafenib group (RR = 3.08, 95%CI [1.38, 6.87], $p=0.006$), the DCR between the HAIC group and the sorafenib group was not significantly different (RR = 0.94, 95%CI [0.60, 1.48], $p=0.798$). As we know, TACE blocks the hepatic artery blood supply of liver cancer and plays an anti-cancer role by inducing tumor ischemia, hypoxia, and necrosis. Hypoxia can up-regulate hypoxia-inducing factor 1 and then up-regulate vascular endothelial growth factor (VEGF) to promote tumor angiogenesis, which is related to tumor refractory to TACE [32-36]. Furthermore, when TACE is not completely effective, it may induce a significant angiogenesis reaction[37]. Sorafenib is a multi-kinase inhibitor of VEGF and platelet-derived growth factor (PDGF) receptors[38]. The better effectiveness of sorafenib in patients with TACE-refractory HCC may be related to its inhibition of tumor angiogenesis[16, 39, 40].

All of the patients in 4 studies[20, 23-25] had no extrahepatic metastasis, while Moriya et al. included patients with extrahepatic metastasis. And the proportion of patients with extrahepatic metastasis included in Moriya et al.'s study[26] was significantly different between the two groups (5% vs. 80%, $p<0.01$). The prognosis of HCC patients with extrahepatic metastasis was significantly worse than that of HCC patients without extrahepatic metastasis [11, 12, 26]. When the study of Moriya et al. was excluded, the results of the meta-analysis in OS did not change significantly (HR = 1.841, 95% CI [1.12, 3.03], $p=0.016$), which means that Moriya et al.'s study did not have a significant influence on the research results. When excluding other studies one by one, the results of the meta-analysis in OS are still stable.

Previous studies suggest that compared with sorafenib, patients in the HAIC group have a lower incidence of AEs in the treatment process and higher safety, especially when HCC is combined with portal vein tumor thrombosis [12, 27, 41]. Both the HAIC group and the sorafenib group, there were cases of discontinuation of treatment due to AEs. Ikeda et al. [24] showed that 9.1% of patients in the HAIC group were discontinued due to AEs, and 14% of patients in the sorafenib group were discontinued due to AEs. The study of Kondo et al. [20] suggested that the rate of discontinuation of treatment due to severe AEs in the sorafenib group was up to 32.5%, while the rate of discontinuation due to AEs in the HAIC group was only 2.3%. It should be noted that HAIC has specific operational difficulties and the risk of infection of the injection device [23], while oral sorafenib is convenient, and patient compliance may be better. And compared with HAIC, sorafenib prolong the overall survive (HR = 1.69, 95% CI [1.09, 2.62], $p=0.018$). Discontinuation of sorafenib therapy due to AEs may not wholly offset the survival benefits of sorafenib compared with HAIC for TACE-refractory HCC. Sorafenib may be more suitable for the treatment of TACE-refractory HCC.

The study has several limitations. First, all the studies included in this study were retrospective studies, and no high-quality randomized controlled trials were included. Second, the small number of studies included, and the small sample size included in each study, may overestimate the efficacy of the treatment. Third, baseline characteristics and treatments were not identical between studies, which may introduce heterogeneity. And due to the small number of studies, it is currently impossible to perform Meta-regression to determine the source of heterogeneity. Finally, the included studies were all from Japan, and most included patients without extrahepatic metastasis [20, 23-25], the generalization of the results may be limited to some extent. In the case of limited clinical evidence, the results of this meta-analysis can provide references for clinicians. Sure, large-scale, high-quality, randomized controlled trials are needed.

Conclusions

Compared with hepatic artery infusion chemotherapy, patients with TACE- refractory HCC in the sorafenib group can obtain significantly longer OS. Sorafenib may be more suitable for the treatment of patients with TACE- refractory HCC. High-quality evidence is needed.

Abbreviations

HAIC: Hepatic Arterial Infusion Chemotherapy; TACE: Transcatheter Arterial Chemoembolization; HCC: Hepatocellular Carcinoma; OS: Overall Survival; PFS: Progression-free Survival; ORR: Objective Response Rate; DCR: Disease Control Rate; HR: Hazard Ratio; CI: Confidence Interval; RR: Risk Ratio; LCSGJ: the Liver Cancer Study Group of Japan; JSH: the Japan Society of Hepatology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS: Newcastle-Ottawa Scale; AEs: Adverse Events; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-derived Growth Factor.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Informed consent for publication was obtained from all participants.

Availability of data and materials: Data and materials are available for sharing if needed.

Competing interests: The authors declare no competing interests for this article.

Authors' contributions: SW conceived the study and carried out literature search and selection, data extraction, statistical analysis, and drafted the manuscript. ST and LP carried out literature search and selection, data extraction, and helped with the statistical analysis. XC participated in coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Funding: This study was not funded.

Acknowledgments: Not applicable.

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Tables

Table 1. Basic characteristics of the included studies

Study	Design	Country	Patient	Evaluation criteria	Group	Age (years)	Male	Etiology (HBV/HCV/other)
Hatook 2016	RCS	Japan	Child-Pugh A, without EHS	RECIST	HAIC (n= 48)	67 [46–84]	91%	15/43/7
					Sorafenib (n= 48)	70 [50–88]	74%	13/40/5
Ikeda 2014	RCS	Japan	Child-Pugh A-B, without EHS	RECIST	HAIC (n= 66)	69 [40–82]	79%	8/45/13
					Sorafenib (n= 48)	71 [53–83]	90%	7/32/9
Kodama 2018	RCS	Japan	Child-Pugh A, without EHS	RECIST	HAIC (n= 67)	68	90%	5/22/3
					Sorafenib (n= 113)	71	75%	11/39/10
Kondo 2015	RCS	Japan	Child-Pugh A-B, without EHS	RECIST	HAIC (n= 44)	71 [54–84]	73%	1/33/10
					Sorafenib (n= 83)	70 [37–88]	89%	15/52/16
Moriya 2018	RCS	Japan	Child-Pugh A, some with EHS	mRECIST	B-HAIC (n= 21)	69 [44–88]	76%	NP
					Sorafenib (n= 45)	73 [43–86]	84%	NP

RCS, Retrospective Cohort Study; EHS , Extrahepatic Spread; RECIST—Response Evaluation Criteria in Solid Tumors; mRECIST, modified Response Evaluation Criteria in Solid Tumors—HAIC—Hepatic Arterial Infusion Chemotherapy—B-HAIC—bi-monthly HAIC—HBV—Hepatitis B Viral Infection—HCV—Hepatitis C Viral Infection; NP, No Report

Table 2. Quality evaluation of cohort studies

Study	Selection				Comparable		Outcome Evaluation			Score
	REC	SNEC	AOE	ONP	COLF	EHS	AO	FLE	AFU	
Hatooka 2016	1	1	1	1	1	1	1	1	1	9
Ikeda 2014	1	1	1	1	1	1	1	1	1	9
Kodama 2018	1	1	1	1	1	1	1	1	1	9
Kondo 2015	1	1	1	1	0	1	1	1	1	8
Moriya 2018	1	1	1	1	1	0	1	1	1	8

REC, Representativeness of the Exposed Cohort; SNEC, Selection of the Non-Exposed Cohort; AOE, Ascertainment of Exposure; ONP, Outcome of Interest Was Not Present at Start of Study; COLF, Comparability of liver function; EHS, Extrahepatic Spread; AO, Assessment of Outcome. FLE, Follow-Up Long Enough; AFU, Adequacy of Follow Up

Figures

Figure 1

The study selection process.

Figure 2

Forest plot of meta-analysis in overall survival (OS) and Progression-free survival (PFS). (A) Forest plot of meta-analysis in OS. (B) Forest plot of meta-analysis in PFS.

Figure 3

Forest plot of meta-analysis in objective response rate (ORR) and disease control rate (DCR). (A) Forest plot of meta-analysis in ORR. (B) Forest plot of meta-analysis in DCR.

Figure 4

Sensitivity analysis and funnel plot in overall survival (OS). (A) Sensitivity analysis in OS. (B) Funnel plot used to test publication bias in OS.