

Comparative effectiveness of interventional therapeutic modalities for unresectable hepatocellular carcinoma: A systematic review and network meta-analysis

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Abstract. It is unclear whether hepatic artery infusion chemotherapy (HAIC) or transcatheter arterial chemoembolization (TACE) is more efficient in the combination therapy of hepatocellular carcinoma (HCC). Head-to-head comparisons among HAIC-related therapies are lacking. For this network meta-analysis, PubMed, EMBASE and Cochrane Library databases were searched up to April 1, 2022. Randomized controlled trials (RCTs) were eligible if they evaluated the use or prolongation of TACE or HAIC in patients with advanced HCC and reported or collected survival data. A network meta-analysis was performed to synthesize data and make direct and indirect comparisons between treatments. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to explore the efficacy of various treatment options on overall survival (OS), odds ratios (ORs) with 95% CI were used for overall response rate (ORR), whereas risk ratios (RRs) with 95% CI were used for serious adverse events (SAEs). The analysis of 7 trials including a total of 1,073 patients found that sorafenib

with HAIC-oxaliplatin improved survival (HR=0.33, 95% CI: 0.25-0.44); the ORR was also improved in patients treated with sorafenib plus HAIC-oxaliplatin and sorafenib plus PF-HAIC (OR=22.18, 95% CI: 10.69-52.56; and OR=2.72, 95% CI: 1.43-5.36, respectively). The incidence of liver injury was elevated in patients treated with sorafenib plus TACE (OR=5.93, 95% CI: 2.70-15.41). However, no differences in the incidences of other SAEs were identified among the treatment groups. The present meta-analysis provides preliminary evidence for the comparative safety and efficacy of HAIC and TACE combined with sorafenib, and indicates the dominance of HAIC-oxaliplatin in HCC interventional therapy. However, high-quality RCTs are required to further confirm the efficacy of HAIC-oxaliplatin. The present study has been registered with PROSPERO (registration no. CRD42021288497).

Introduction

Hepatocellular carcinoma (HCC) is currently the sixth most frequently occurring malignant tumor and ranks fourth in terms of cancer-related mortality (1). Sorafenib, an oral tyrosine kinase inhibitor, has been associated with increased survival in patients with HCC (2). However, because 12-32% of patients with HCC have vascular invasion as well as distant metastases at diagnosis (3), the efficacy of sorafenib in these patients is limited (4,5). As a result, combination therapy may be more beneficial. Current therapy options include vascular interventions, local ablation therapy, external radiation therapy, targeted drug therapy, immunotherapy and systemic chemotherapy (6). Hepatic arterial intervention therapy is widely used for its benefits, which include improved tumor-targeting ability, reduced effect on surrounding normal tissues and a lower incidence of serious adverse events (SAEs). However, using transcatheter arterial chemoembolization (TACE) to achieve complete embolization in the treatment of giant HCC is challenging and may increase the incidence of SAEs; additionally, multiple TACE interventions may cause liver injury and negatively affect patient prognosis (7). Hepatic artery infusion chemotherapy (HAIC) with portal vein tumor thrombosis (PVTT) is recommended as the first-line treatment for

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Abbreviations: ORR, overall response rate; 5-FU, 5-fluorouracil; FOLFOX, 5-FU, leucovorin and oxaliplatin; HAIC, hepatic artery infusion chemotherapy; TACE, transcatheter arterial chemoembolization; HCC, hepatocellular carcinoma; PF, cisplatin and 5-FU; RCT, randomized controlled trial; CDDP, cisplatin-HAIC; SorCDDP, sorafenib with CDDP; PVTT, portal vein tumor thrombosis; DIC, deviance information criterion; AEs, adverse events; SAEs, serious AEs; VEGF, vascular endothelial growth factor

Key words: hepatocellular carcinoma, hepatic artery infusion chemotherapy, transcatheter arterial chemoembolization, efficacy, combination therapy

HCC in Japan due to its stability, safety and high conversion rate (8). Moreover, its efficacy in large HCC has been shown to be superior to that of TACE in other studies (9,10).

Although the overall response rate (ORR) of cisplatin and 5-fluorouracil (5-FU)-based HAIC (PF-HAIC), the most commonly used HAIC regimen in Japan, can reach 27.6 to 40.5% (11), it is questionable whether HAIC is superior to TACE in combination therapy. A previous meta-analysis showed that HAIC combined with sorafenib was not effective in prolonging survival compared with sorafenib alone (12), while a meta-analysis by Li *et al* (13) demonstrated that TACE combined with sorafenib significantly prolonged survival compared with sorafenib alone, despite a greater number of reported adverse events (AEs) during treatment. Given that these studies included patients with advanced HCC, whether high-dose chemotherapy is more effective than vascular embolization is debatable. Studies conducted in recent years have shown that the clinical efficacy of HAIC-oxaliplatin is much improved when used as a combination therapy. A head-to-head study of 5-FU, leucovorin and oxaliplatin (FOLFOX)-HAIC vs. TACE also demonstrated a clear advantage of the former in terms of efficacy and safety (14); however, numerous questions remain regarding this study (15,16). Therefore, additional randomized controlled trials (RCTs) are warranted to determine whether the efficacy of HAIC is influenced by the treatment modality or therapeutic regimen.

There is a lack of evidence from trials in which different interventional modalities and various regimens for HAIC have been directly compared; thus, a network meta-analysis can assist in the comparison of two or more therapies that have not been directly compared. In the present study, to aid physicians in the selection of appropriate interventions and regimens, HCC was stratified into primary and secondary cancers due to their different pathogenesis, and only clinical prospective RCTs related to primary HCC were included to eliminate bias in the analysis. A network meta-analysis of the included RCTs was performed to assess the survival and incidence of AEs in patients with unresectable liver cancer receiving different HAIC regimens or TACE.

Materials and methods

Protocol and registration. The present study followed the PRISMA guidelines (17) and was preliminarily registered on PROSPERO (registration no. CRD42021288497). The systematic review was conducted in accordance with the previously established protocol outlined in Appendix S1.

Literature retrieval process. Potentially relevant and eligible studies published before April 2022 were systemically retrieved from electronic databases including PubMed, Cochrane Library and Embase. The PubMed database was searched with keywords including ‘unresectable hepatocellular carcinoma’, ‘unresectable HCC’, ‘HAIC’, ‘hepatic arterial infusion chemotherapy’, ‘TACE’ and ‘transcatheter arterial chemoembolization’. The search strategy is detailed in Appendix S2.

Study inclusion and exclusion criteria. The study inclusion criteria were as follows: RCTs; studies that included patients

diagnosed with advanced HCC; studies with complete data on methodology, patients’ characteristics, AEs and overall survival (OS); and studies comparing ≥ 2 arms that consisted of the modalities of interest, including sorafenib alone, TACE with sorafenib, and HAIC with sorafenib. The study exclusion criteria were as follows: Letters to the editor, study protocols, conference abstracts, case reports, non-RCTs, animal studies, editorials and posters. In addition, only reports in English were included in the study.

Literature screening. Two reviewers (XLC and HCY) independently evaluated all titles and abstracts. Additionally, all references cited by enrolled studies were manually reviewed to identify additional potentially eligible studies. Articles were further screened in a stepwise fashion according to their abstract and then full-text using the aforementioned inclusion and exclusion criteria. Any disagreements were resolved through consensus and the opinion of a third reviewer (QGF).

Data extraction and quality assessment. The first author's name, publication year, population characteristics, number of patients in each treatment arm and outcomes including OS, ORR, SAEs, hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted. Moreover, information about the trial design, interventions and comparators, statistical analysis, primary and secondary outcomes and quality of life outcomes were also retrieved.

Risk of bias assessment and data analyses. De-duplication of retrieved documents was performed via EndNote X9 (Clarivate). The quality of the included studies was assessed using the Cochrane risk of bias tool (version 5.1.0; The Cochrane Institute). Two reviewers (XLC and HCY) evaluated each study for bias and rated it as follows: Low risk of bias, high risk of bias or unclear. Unclear was defined as either the lack of information to determine bias or uncertainty for bias.

The network meta-analysis was conducted in R package (4.1.2) using the gemtc package (1.0-1). This package uses a Bayesian Markov chain Monte Carlo sampler to run the model with 50,000 adaptation or ‘burn-in’ samples followed by 100,000 samples without thinning. Model convergence was established by the visual inspection of Brook-Gelman Rubin plots. As the analyses used a contrast-based approach for OS data, the analysis assumed that the data conformed to the proportional hazards assumption. Certain survival data were extracted from the survival curves according to the methods described by Parmar *et al* (18) and Wang and Zeng (19). Methods were as described in the Cochrane Handbook for Systematic Reviews of Interventions (20). For Kaplan-Meier data, the proportional hazards assumption was tested by fitting a Cox proportional hazards regression model to the time-to-event data and assessing whether the Schoenfeld residuals from the Cox model were independent of time. HRs with 95% CIs were calculated to explore the efficacy of various treatment options on OS, odds ratios (ORs) with 95% CI were used for ORR, whereas risk ratios (RRs) with 95% CI were used for SAEs.

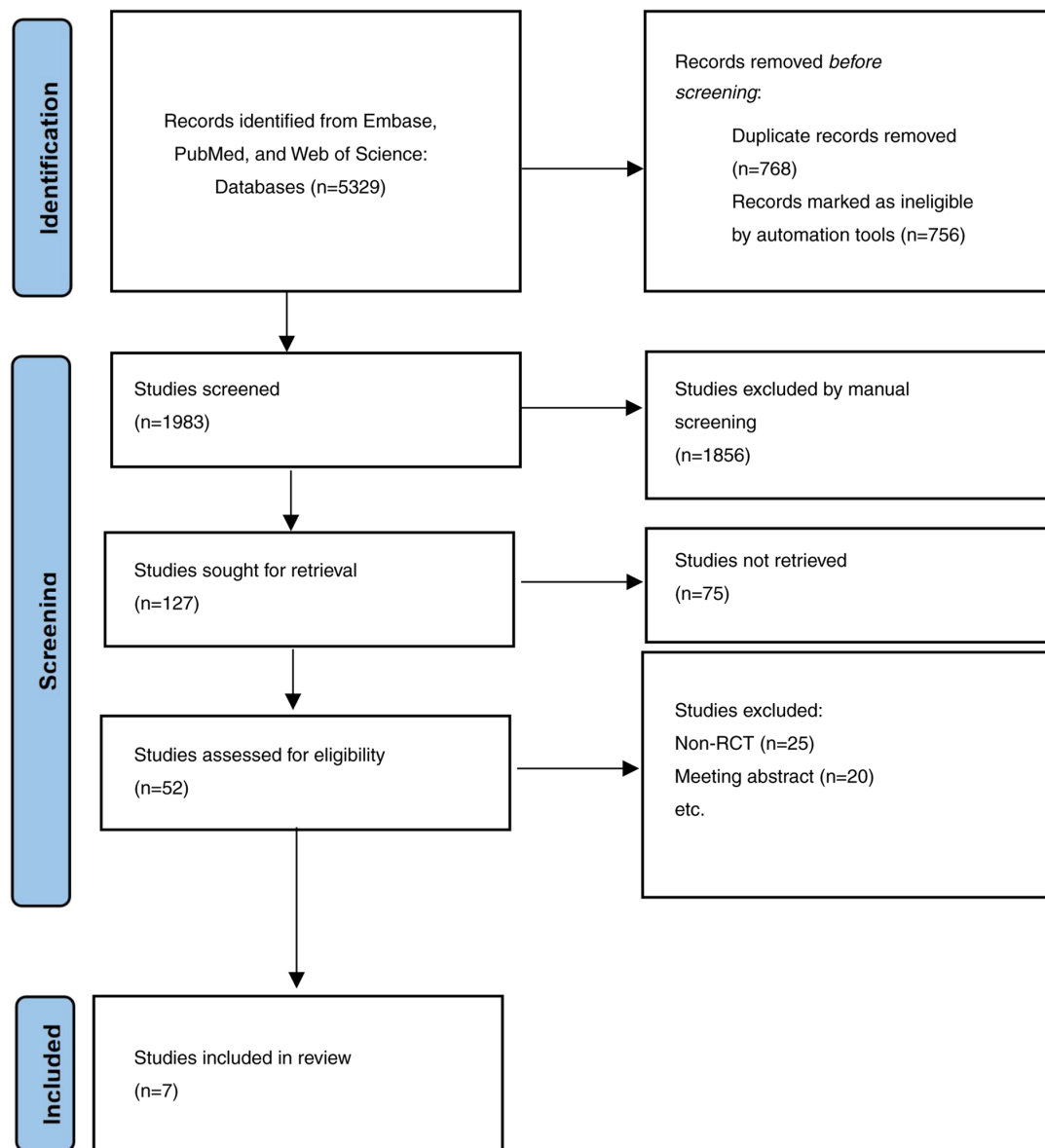


Figure 1. Flow chart of the search strategy. RCT, randomized control trial.

Results

Screening. A total of 5,329 articles were retrieved for this study. EndNote X9 was used to eliminate 3,256 duplicates. A further 1,931 articles were excluded by reading the titles and abstracts. After reading 52 accessible articles in full, 20 articles related to trial registration and 25 retrospective studies were excluded. Eventually, a total of 7 studies (21-27) involving 1,073 patients were included, as presented in Fig. 1.

Risk of bias assessment. Based on the Cochrane risk of bias tool, the methodological quality of the included studies was fair, as demonstrated in Table S1 and Fig. S1. All 7 studies had adequate outcome measurement, enrolled a representative sample of patients and had a reasonable length of follow-up.

Characteristics of included studies. Table I presents the characteristics of the included studies. The 7 studies

included a total of 1,073 patients (sorafenib alone, n=517; sorafenib plus HAIC, n=359; sorafenib plus TACE, n=197), of whom 925 were male and 148 were female. The most common etiology of HCC was hepatitis B virus infection [sorafenib plus HAIC, 49.86% (179/359); sorafenib alone, 57.25% (296/517); sorafenib plus TACE, 77.66% (153/197)], followed by hepatitis C virus infection [sorafenib plus HAIC, 26.18% (94/359); sorafenib alone, 22.24% (115/517); sorafenib plus TACE, 5.0% (10/197)]. Furthermore, 26.74% (96/359) patients treated with sorafenib plus HAIC, 18.96% (98/517) patients treated with sorafenib alone and 39.59% (78/197) treated with sorafenib plus TACE group had extrahepatic metastases. Only the studies by He *et al* (22), Zheng *et al* (21) and Lee *et al* (27) observed a statistically significant difference in OS between the two groups being compared in the respective study (HR=0.35, 95% CI: 0.26-0.48; HR=0.28, 95% CI: 0.15-0.53; and HR=0.59, 95% CI: 0.84-0.48, respectively). Since Lee *et al* (27) did not report the HR values with a 95% CI, the aforementioned

Table I. Characteristics of included studies.

Author, year	Country	ECOG	Group	Interventional therapy details	mOS, months	N	Sex (M/F)	Age, years	Tumor size, cm	No. of tumors (single/multiple)	PVTT	Child-Pugh	BCLC	Data time frame	(Refs.)
Ikeda, 2016	Japan	0-1	SorCDDP	Cisplatin (65 mg/m ²)/4-6 weeks	10.6	65	56/9	49 (41-55)	10.1 (7.7-13.2)	30/95	40/25	5-6	NA	June 2011-December 2013	(25)
Kudo, 2018	Japan	0-1	Sorafenib alone	400 mg twice daily	8.7	41	32/9	49 (40-56)	10.1 (8.3-12.1)	33/89	17/24				
			Sorafenib + PF-HAIC	Cisplatin (20 mg/m ²) on days 1 and 8 + 5-FU (330 mg/m ²) on days 1-5 and 8-12/28 days	11.8	102	89/13	69 (62-75)	NA	NA	58/44	5-7	0/32/70	November 2010-June 2014	(24)
Kondo, 2019	Japan	0-1	Sorafenib alone	400 mg twice daily	11.5	103	88/15	68 (62-75)			64/39		0/27/76		
			SorCDDP	Cisplatin (65 mg/m ²)/4-6 weeks	15.2	35	28/7	72 (65-79)	NA	NA	21/14	5-7	2/14/19	August 2011-November 2014	(23)
			Sorafenib alone	400 mg sorafenib twice daily	10.0	33	27/6	70.9 (61.8-80)			22/11		2/13/18		
He, 2019	China	0-2	Sorafenib + FOLFOX-HAIC	Oxaliplatin (85 mg/m ²) + leucovorin (400 mg/m ²) + 5-FU (400 mg/m ²); 5-FU infusion 2,400 mg/m ² for 46 h/3 weeks	13.4	125	111/14	49 (41-55)	10.1 (7.7-13.2)	30/95	125/0	5-6	NA	April 2016-October 2017	(22)
Zheng, 2022	China	0-2	Sorafenib alone	400 mg twice daily	7.1	122	112/10	49 (40-56)	10.1 (8.3-12.1)	33/89	122/0				
			Sorafenib + HAIC	Oxaliplatin (35 mg/m ²) + 5-FU (600 mg/m ²) + leucovorin (200 mg/m ²) injected intravenously/28 days	16.3	32	30/2	56 (45-67)	10.6 (6.6-14.6)	15/17	32/0	5-7	NA	June 2017-November 2019	(21)
Lee, 2020	China	0-2	Sorafenib	400 mg twice daily	6.5	32	31/1	55 (45-65)	10.7 (6.8-14.6)	12/20	32/0				
			Sorafenib + TACE	Lipiodol + 10-20 mg Adriamycin/elution beads + Adriamycin/2-3 months	11.0	27	23/4	60 (53-65.5)	6.2 (3.5-13.5)	NA	11/16	5-7	NA	NA	(27)
Park, 2018	South Korea	0-2	Sorafenib	200-400 mg twice daily	5.0	17	15/2	59 (51-62)	6.5 (3.4-12.5)		5/12				
			Sorafenib + TACE	Doxorubicin or cisplatin + embolization materials/28 days	12.8	170	136/34	60.2 (50.6-69.8)	NA	NA	68/102	5-7	3/39/128	January 2013-December 2015	(26)
			Sorafenib	200-400 mg twice daily	10.8	169	147/22	61.3 (51.7-70.9)			63/106		0/4/125		

Continuous variables are expressed as median (range). ECOG: Eastern Cooperative Oncology Group; mOS, mean overall survival; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer; SorCDDP, sorafenib with cisplatin-HAIC; HAIC, hepatic artery infusion chemotherapy; PF-HAIC, 5-FU-based HAIC; 5-FU, 5-fluorouracil; FOLFOX, 5-FU, leucovorin and oxaliplatin; TACE, transcatheter arterial chemoembolization; NA, not available.

data were extracted from the Kaplan-Meier curve provided in the article. All 7 studies enrolled HCC patients with PVTT, and all included patients were unsuitable for curative resection or local ablation.

Network meta-analysis. The 7 RCTs identified through the literature reviews enabled the creation of a seven-node network with two edges, which included sorafenib alone, sorafenib with cisplatin-HAIC (CDDP) (SorCDDP), sorafenib with HAIC-oxaliplatin, sorafenib with TACE, and sorafenib with PF-HAIC. Fig. 2 shows the network meta-analysis (NMA) map of the interventional therapies in the studies that were directly compared for efficacy in prolonging survival. According to deviance information criterion (DIC) and total residual deviance statistics, the I^2 value was much higher than 50%, and the random-effects model had a superior fit to the data than the fixed-effects model, with the former model having fewer parameters and a lower DIC (28). It was not possible to assess inconsistency within the network due to the absence of any closed loops. The proportional hazards assumption was not violated in the studies with time-to-event data. The Kaplan-Meier curves in all 7 RCTs crossed over; however, violation of the proportional hazards assumption was not supported by the statistical data.

Efficacy. The NMA revealed a significant difference between the sorafenib plus HAIC-oxaliplatin regimen and other treatment strategies in terms of OS (HR=0.33, 95% CI: 0.25-0.44). By contrast, comparisons between sorafenib plus PF-HAIC, SorCDDP and sorafenib plus TACE identified little difference with mortality HRs of 1.01 (95% CI: 0.74-1.38), 1.22 (95% CI: 0.88-1.71) and 0.79 (95% CI: 0.62-1.01), respectively. Fig. 3 depicts the ranking of the treatments with regard to the likelihood of being the superior treatment. Rank probability plots revealed that there would be a 99.9% likelihood of sorafenib plus FOLFOX-HAIC being the most effective treatment, followed by sorafenib plus TACE at 86.6% and SorCDDP at 75.6%. Furthermore, a comparison based on mRECIST criteria found that patients treated with sorafenib plus FOLFOX-HAIC had significantly higher ORR than those receiving other treatment regimens (OR=22.0, 95% CI: 10.6-25.7).

SAEs. The analysis of SAEs revealed that the risk of liver injury was higher in the sorafenib plus TACE group compared with other groups (HR=5.93, 95% CI: 2.70-15.41); there was no significant difference in the risk of liver injury between patients receiving sorafenib plus HAIC compared with those receiving sorafenib alone. Furthermore, no significant differences in the constitutional symptoms and gastrointestinal reactions were detected between all the treatment groups. Table II summarizes the results of the network meta-analyses regarding OS, ORR and SAEs.

Discussion

Due to the lack of clinical RCTs in which different treatments of HCC are directly compared, the present meta-analysis used 7 RCT studies to indirectly evaluate the efficacy and

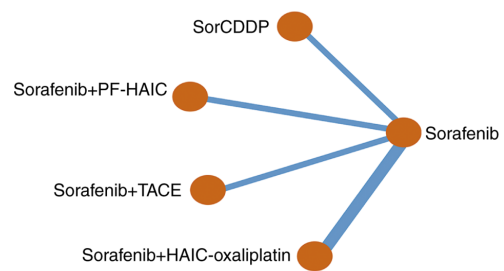


Figure 2. Network of the available direct comparisons in the included studies. SorCDDP, sorafenib with cisplatin-HAIC; PF-HAIC, 5-fluorouracil-based HAIC; TACE, transcatheter arterial chemoembolization; HAIC, hepatic artery infusion chemotherapy.

safety of CDDP, PF-HAIC, HAIC-oxaliplatin and TACE as interventional modalities when combined with sorafenib.

The study findings revealed that combining CDDP, PF-HAIC and TACE with sorafenib did not significantly differ from sorafenib alone in terms of OS, indicating that inappropriate treatment modalities and regimens are not beneficial to HCC patient survival. However, the prognosis of patients receiving HAIC-oxaliplatin plus sorafenib was found to be significantly improved when compared with other treatment modalities. The survival benefit may be explained in part by the superior efficacy of oxaliplatin in HCC treatment. Compared with cisplatin, oxaliplatin has significantly improved pharmacokinetic, biochemical, cytotoxic and immunological properties (29). Oxaliplatin is an inhibitor of ribosomal RNA synthesis, which induces ribosome biogenesis stress during the active translation of RNA interference. Thus, oxaliplatin exerts its cytotoxic effects by inhibiting protein synthesis rather than via a DNA damage response (30). In addition, oxaliplatin induces antitumor immune responses to anthracyclines via the stimulation of pro-apoptotic cell calreticulin exposure, leading to immunogenic tumor cell death (31). Notably, sorafenib normalizes HCC vasculature and increases drug transport by interacting with platinum transporter proteins to increase the local enrichment of the oxaliplatin concentration in tumors (32). As a result, a multidrug combination based on oxaliplatin may be superior to cisplatin alone. The present findings indirectly support a previous study suggesting that HAIC-oxaliplatin plus sorafenib has greater efficacy than TACE for large HCC (≥ 7 cm) (14). It is hypothesized that this may be because the prolonged and continuous infusion of chemotherapeutic agents through the target artery increases the local drug concentration and tumor uptake compared with systemic intravenous chemotherapy (33). In addition, there may be a synergistic antitumor effect between sorafenib, oxaliplatin and 5-FU. Sorafenib has several targets, including Raf-1, vascular endothelial growth factor (VEGF) receptor 1-3 and platelet-derived growth factor receptor- β ; the inhibition of Raf-1 can induce apoptosis and counteract the resistance of tumor cells to FOLFOX (34,35). It has been shown that 5-FU, in particular, increases tumor sensitivity to oxaliplatin by increasing multidrug resistance-associated protein 2 mRNA expression, and its synergistic efficacy with oxaliplatin mediates the expression of drug transporter proteins (22). TACE plus

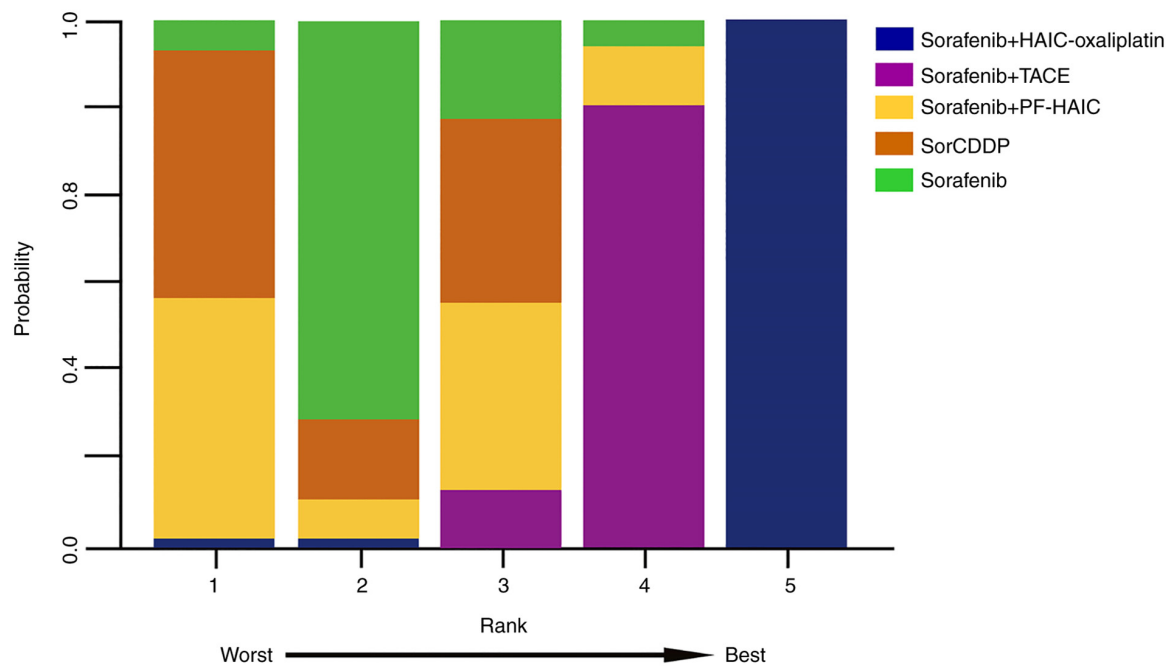


Figure 3. Rankogram of treatment modality. HAIC, hepatic artery infusion chemotherapy; TACE, transcatheter arterial chemoembolization; PF-HAIC, 5-fluorouracil-based HAIC; SorCDDP, sorafenib with cisplatin-HAIC.

sorafenib is more effective than traditional HAIC, which is likely due to the tumor microenvironment created by TACE treatment-induced ischemia and hypoxia, which causes the upregulation of local inflammatory factors, including insulin-like growth factor-2 and VEGF (36). Moreover, sorafenib inhibits tyrosine kinases of the VEGF signaling pathway, inhibiting tumor angiogenesis and weakening the proliferation ability of tumor cells (37). The combination of sorafenib with TACE can improve patient survival, since sorafenib promotes the deposition of the drug-eluting TACE component lipiodol in HCC vessels, where it exhibits a tumor necrotizing effect (38). TACE induces ischemia and hypoxia in tumor tissues by the targeted embolization of arteries during treatment; however, this effect requires hepatic vein patency to ensure normal tissue metabolism, and since ischemic and hypoxic conditions may favor the resistance of tumor cells to therapeutic agents (39), promoting angiogenesis and the migration of certain cytokines, for example IL-8, this may lead to tumor metastasis (40). HAIC, by contrast, is continuously administered throughout the treatment process, and tumor cells are killed via a cytotoxic response, without any dependence of normal tissue metabolism on the hepatic vein and the resistance and metastasis induced by inflammatory factors. Therefore, HAIC may be a more effective and safer intervention for HCC than TACE. Nevertheless, more studies are required to clarify and demonstrate whether this efficacy is due to interventional modalities or the regimen used. Based on the current findings, we hypothesize that HAIC-oxaliplatin currently is a superior interventional combination therapy for HCC. However, whether this efficacy advantage is due to the type of treatment or the drug combination remains unclear and requires validation in high-quality head-to-head studies.

A comparison of the various SAEs in the present meta-analysis revealed that patients treated with TACE plus sorafenib had an elevated risk of liver injury. This could be because TACE and its associated metabolites stimulate the expression of pro-apoptotic genes and the activation of multiple death signaling pathways, thereby promoting apoptosis and inducing an inflammatory response that accelerates the progression of drug-induced liver injury. Moreover, embolic agents are able to enter small arteries and capillaries in non-cancerous areas, causing ischemia and hypoxia in normal tissues and exacerbating oxidative stress and liver injury (41). Furthermore, patients with HCC who have intrahepatic metastases typically have a history of hepatitis and cirrhosis, and their liver function is already compromised (42). According to previous research, liver injury frequently occurs in colorectal cancer-related chemotherapy using the FOLFOX regimen, most likely due to the toxicity of oxaliplatin metabolites, which affects the permeability of the hepatic sinusoidal cells and raises the pressure in the hepatic venous sinusoids, resulting in liver injury and sinusoidal portal hypertension (43,44). However, the present study indicates that HAIC-oxaliplatin plus sorafenib is significantly safer than TACE when combined with sorafenib. Regarding constitutional symptoms and gastrointestinal events, we hypothesize that patients with HCC who are treated with HAIC-oxaliplatin are at a higher risk of SAEs because they have a heavier tumor burden. Notably, the incidence of overall SAEs suggests that HAIC-oxaliplatin may be more appropriate than TACE and other HAIC therapies in the combination treatment of patients with a heavier tumor burden.

The combination of interventional therapy and oral drugs has markedly improved the survival of patients with advanced HCC. The REFLECT trial established the first-line

Table II. Comparisons of efficacy in terms of OS and severe adverse events in advanced hepatocellular carcinoma.

A, OS [HR (95% CI)]						
Author, year	Treatment group	Sorafenib + HAIC-oxaliplatin	Sorafenib + TACE	Sorafenib + PF-HAIC	SorCDDP	(Refs.)
Zheng, 2022; He, 2019	Sorafenib + HAIC-oxaliplatin	-	-	-	-	(21,22)
Park, 2018; Lee, 2020	Sorafenib + TACE	0.42 (0.29-0.62)	-	-	-	(26,27)
Kudo, 2018	Sorafenib + PF-HAIC	0.33 (0.22-0.50)	0.78 (0.52-1.17)	-	-	(24)
Kondo, 2018; Ikeda, 2016	SorCDDP	0.27 (0.18-0.42)	0.64 (0.42-0.97)	0.83 (0.52-1.30)	-	(23,25)
All of the above	Sorafenib (Control)	0.33 (0.25-0.44)	0.79 (0.62-1.01)	1.01 (0.74-1.38)	1.22 (0.88-1.71)	(21-27)
B, Overall response rate [OR (95% CI)]						
Author, year	Treatment group	Sorafenib + HAIC-oxaliplatin	Sorafenib + TACE	Sorafenib + PF-HAIC	SorCDDP	(Refs.)
Zheng, 2022; He, 2019	Sorafenib + HAIC-oxaliplatin	-	-	-	-	(21,22)
Park, 2018; Lee, 2020	Sorafenib + TACE	9.26 (3.03-29.26)	-	-	-	(26,27)
Kudo, 2018	Sorafenib + PF-HAIC	8.16 (3.01-23.79)	0.88 (0.32-2.54)	-	-	(24)
Kondo, 2018; Ikeda, 2016	SorCDDP	7.73 (2.05-27.81)	0.83 (0.22-2.96)	0.95 (0.27-3.03)	-	(23,25)
All of the above	Sorafenib (Control)	22.18 (10.69-52.56)	2.4 (1.10-5.58)	2.72 (1.43-5.36)	2.88 (1.12-8.58)	(21-27)
C, Liver injury [OR (95% CI)]						
Author, year	Treatment group	Sorafenib + HAIC-oxaliplatin	Sorafenib + TACE	Sorafenib + PF-HAIC	SorCDDP	(Refs.)
Zheng, 2022; He, 2019	Sorafenib + HAIC-oxaliplatin	-	-	-	-	(21,22)
Park, 2018; Lee, 2020	Sorafenib + TACE	0.22 (0.07-0.68)	-	-	-	(26,27)
Kudo, 2018	Sorafenib + PF-HAIC	1.34 (0.49-3.81)	5.98 (2.07-19.30)	-	-	(24)
Kondo, 2018; Ikeda, 2016	SorCDDP	1.35 (0.51-3.62)	6.02 (2.17,18.53)	1.01 (0.39-2.55)	-	(23,25)
All of the above	Sorafenib (Control)	1.34 (0.64-2.90)	5.93 (2.70-15.41)	1.00 (0.49-2.00)	0.99 (0.54-1.86)	(21-27)
D, Constitutional symptoms [OR (95% CI)]						
Author, year	Treatment group	Sorafenib + HAIC-oxaliplatin	Sorafenib + TACE	Sorafenib + PF-HAIC	SorCDDP	(Refs.)
Zheng, 2022; He, 2019	Sorafenib + HAIC-oxaliplatin	-	-	-	-	(21,22)
Park, 2018; Lee, 2020	Sorafenib + TACE	1.47 (0.35-6.59)	-	-	-	(26,27)
Kudo, 2018	Sorafenib + PF-HAIC	1.39 (0.33-6.23)	0.94 (0.25-3.65)	-	-	(24)
Kondo, 2018; Ikeda, 2016	SorCDDP	0.53 (0.06-3.41)	0.36 (0.04-2.07)	0.38 (0.04-2.15)	-	(23,25)
All of the above	Sorafenib (Control)	1.81 (0.63-5.92)	1.24 (0.48-3.28)	1.31 (0.52-3.40)	3.36 (0.83-25.50)	(21-27)

Table II. Continued.

E, Gastrointestinal reactions [OR (95% CI)]						
Author, year	Treatment group	Sorafenib + HAIC-oxaliplatin	Sorafenib + TACE	Sorafenib + PF-HAIC	SorCDDP	(Refs.)
Zheng, 2022; He, 2019	Sorafenib + HAIC-oxaliplatin	-	-	-	-	(21,22)
Park, 2018; Lee, 2020	Sorafenib + TACE	0.72 (0.22-2.35)	-	-	-	(26,27)
Kudo, 2018	Sorafenib + PF-HAIC	2.05 (0.59-8.51)	2.86 (0.63,14.83)	-	-	(24)
Kondo, 2018; Ikeda, 2016	SorCDDP	0.57 (0.07-3.35)	0.78 (0.08-5.63)	0.27 (0.03-2.05)	-	(23,25)
All of the above	Sorafenib (Control)	0.9 (0.49-1.63)	1.24 (0.45-3.53)	0.44 (0.12-1.30)	1.57 (0.30-12.06)	(21-27)

The HR values in the table are the treatment modality in the horizontal coordinate compared to the treatment modality in the vertical coordinate. HR, hazard ratio; CI, credible interval; OR, odds ratio; HAIC, hepatic artery infusion chemotherapy; TACE, transcatheter arterial chemoembolization; PF-HAIC, 5-fluorouracil-based HAIC; SorCDDP, sorafenib with cisplatin-HAIC; OS, overall survival.

status of lenvatinib (45), and Ding *et al* (46) demonstrated its superior efficacy compared with sorafenib in HCC combination therapy. Regorafenib and cabozantinib, which are the second-line drugs for advanced HCC, were also approved following the RESORCE and CELESTIAL trials (47,48). With the development of drug-eluting beads and the advancement of super-selective TACE (2,49), further studies are recommended to investigate the efficacy of these new oral drugs in combination with interventional modalities for advanced HCC.

There are several limitations to the present study. Firstly, only 7 RCTs met the inclusion criteria of the meta-analysis, and the potential bias of the studies could impact the results. Furthermore, because the pathogenesis and prevalence of hepatitis vary greatly across different regions and populations, the fact that the population in this study comprises only Asian patients may limit the generalizability of the study findings.

In conclusion, the present study indicates that in patients with advanced primary HCC, HAIC-oxaliplatin significantly improves patient survival when combined with sorafenib compared with other regimens or interventional modalities. Although there may be significant bias in assessing outcome indicators due to patient enrollment differences, the results suggest that the HAIC-oxaliplatin plus sorafenib combination should be more widely used. However, the study of HAIC dosing regimens for advanced HCC and exploration of combination treatment options in the future studies is recommended.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

XLC and HCY conceived and designed the research. XLC, HCY and QGF performed data acquisition, data analysis and manuscript preparation. QY, WKJ, SZR and WCZ assisted with data acquisition, data analysis and statistical analysis. WCZ and SZR confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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