

Hepatic arterial infusion chemotherapy versus Sorafenib for advanced hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis

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Research

Keywords: Sorafenib, Hepatic arterial infusion chemotherapy, hepatocellular carcinoma, Portal vein tumor thrombus

Posted Date: February 24th, 2020

DOI: <https://doi.org/10.21203/rs.2.24267/v1>

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Abstract

Background : Hepatocellular carcinoma (HCC) is ranked as the sixth most common solid cancer and the third leading cause of cancer-related death in the world. Sorafenib is the first line systematic treatment for patients with advanced HCC. Hepatic arterial infusion chemotherapy (HAIC) has been proved to be an effective treatment for advanced HCC. Here, we conducted a meta-analysis to compare the efficacy of HAIC versus sorafenib of advanced HCC patients with PVTT.

Methods : The databases of MEDLINE (PubMed), Cochrane Library, EMBASE, and Web of Science were systematically searched for retrieving the relevant publications before 31 July 2019. The endpoint included overall survival (OS), time to progression (TTP), partial response rate (PRR), complete response rate (CRR), objective response rate (ORR), stable disease rate (SDR).

Results : A total of three studies involving 214 advanced HCC patients with PVTT enrolled in this meta-analysis. HAIC significantly improved TTP (hazard ratio (HR)=0.56, 95% CI: 0.39-0.82; P=0.003), PRR (odds ratio (OR)=3.31, 95% CI: 1.46-7.50; P=0.004), ORR (OR=3.78, 95% CI: 1.68-8.50; P=0.001) compared to sorafenib. However, no significant difference was found in OS (HR=0.77, 95% CI: 0.56-1.06, p=0.11), CRR (OR=2.54, 95% CI: 0.39-16.47; P=0.33), SDR (OR=1.48, 95% CI: 0.43-5.08; P=0.001).

Conclusions : This meta-analysis suggested that HAIC provides better TTP, PRR, ORR than sorafenib for patients of advanced HCC with PVTT. Therefore, we recommend HAIC as a potential therapy for advanced HCC patients with PVTT. However, owing to the above limitations, more high-quality studies are warranted to evaluate this finding.

Background

Hepatocellular carcinoma is ranked as the sixth most common solid cancer and the third leading cause of cancer-related death in the world. With 841,080 new cases of liver cancer diagnosed per year and 781,631 deaths in 2018[1, 2]. The prognosis of hepatocellular carcinoma is poor, with a 5-year survival rate of 15%-17%[3]. Hepatectomy, liver transplantation, ablation, transhepatic arterial chemoembolization

(TACE), sorafenib, hepatic arterial infusion Chemotherapy (HAIC), are potentially curative therapies for HCC patients. Although hepatic resection has been considered as preferred management for early stage patients, only approximately 30% patients were in an early stage at the time of diagnosed. However, more than 70% of hepatocellular carcinoma are diagnosed during the advanced stage of the disease, with a median overall survival (OS) time of 7 months and surgery resection is not suitable[4, 5]. About 10%-40% of patients with advanced hepatocellular carcinoma concurrent portal vein tumor thrombus (PVTT) at the time of diagnosis[6]. If not treated with any interventions, the median OS is about 2–4 months of the advanced HCC patients with PVTT but 24.4 month for those without PVTT[7–9]. Therefore, PVTT is usually indicate poor prognosis in patients with HCC.

Sorafenib is an oral multitarget tyrosine kinase inhibitor, which inhibits the Raf pathway and vascular endothelial growth factor (VEGF) pathway[10]. Sorafenib is the first line systematic treatment for patients with advanced HCC recommended by the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (AASLD), which achieves a modest survival benefit for advanced HCC patients[11, 12]. According to the two multicenter, phase 3, double-blind, placebo-controlled trial (the SHARP trial and the Asia-Pacific trial), sorafenib significantly improve median overall survival and delayed the median TTP, compared placebo. SHARP trial demonstrates a median OS of 10.7 in the sorafenib group and 7.9 months in the placebo group, the median TTP was 5.5 versus 2.8 months, respectively. In the Asia-Pacific trial, the median OS in the sorafenib and placebo groups was 6.5 months and 4.2 months, the median TTP in the two groups was 2.8 months and 1.4 months, respectively[13, 14]. However, due to the limited efficacy, the severe adverse event for certain people and drug resistance, some reports demonstrated unsatisfactory results of sorafenib and restricted the application of this drug [15–17]. Thus, there is urgent to find out an effective and safe treatment method for advanced HCC patients.

Hepatic arterial infusion chemotherapy (HAIC) has been proved to be an effective treatment for advanced HCC in Asia, especially in Japan[18]. In HAIC, anticancer drugs are directly injected into the liver via the hepatic artery through the use of an implantable port system. Compared with systemic chemotherapy, HAIC is theoretically achieved a highly concentrated chemotherapeutic agents in the liver which provide a stronger antitumor effect with lower adverse reactions[19]. Several studies have reported HAIC achieved higher objective response rate (ORR) and consequent survival benefits than sorafenib monopoly[20–22]. Although HAIC is effective and is strongly recommended for advanced HCC patients with portal vein invasion (Vp1-4) by the JSH-LCSGJ guideline[23]. However, HAIC is not recommended as stand treatment in the world.

A previous meta-analysis evaluated the safety and efficacy of HAIC versus Sorafenib treated for advanced HCC and suggested HAIC for the treatment of advanced HCC[24]. However, there still lack sufficient evidence to support the wide use of HAIC for the treatment of advance HCC with PVTT. Herein, this study is aim to performed a systematic review and meta-analysis of all available studies to compared the efficacy of HAIC and sorafenib for the treatment of advanced HCC patients with PVTT.

Methods

Searching strategy

From inception to 30 July 2019, comprehensive electronic searches were performed with the database of MEDLINE (PubMed), Cochrane Central Register of Controlled Trials, EMBASE, Web of Science. The search terms and strategy were based on the combination of the following keyword: (“hepatocellular carcinoma” or “liver cancer” or “HCC”) AND (“sorafenib” or “Nexavar”) AND (“hepatic arterial infusion chemotherapy” or “HAIC”). The searching language was restricted to English.

Date extraction and quality assessment

Two reviewers (GQOY and YRW) independently extracted and assessed all data from each study. Any disagreement between two the authors was resolved by discussion and consensus. The following data were extracted: (1) The first author's name, year of publication, gender distribution, study design, treatment group, number of patients, patients' characteristics. (2) The outcome of treatment, such as OS, TTP, PRR, CRR, ORR, SDR.

Criteria for inclusion and exclusion

The inclusion criteria were followed: (1) age 18-75 years; (2) clinical diagnosed advanced HCC with Vp2-Vp4 of PVTT; (3) Child-Pugh A; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (5) White blood cell count $\geq 2.0 \times 10^9/L$ and platelet count $\geq 50 \times 10^9/L$. The exclusion criteria were follows: (1) other serious medical conditions, such as cardiopulmonary and renal insufficiency, infection disease. (2) pregnant women, lactating women; (3) other chemotherapy treatments such as systemic chemotherapy.

Statistical analysis

All analyses were performed strictly with Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, UK). The primary endpoints of OS and TTP were evaluated by using hazard ratio (HR) with a 95% confidence interval (CI). The HR with 95% CI were estimated directly or indirectly from the reported data. If a study only provided a Kaplan-Meier curve, the HR and 95% CI were extracted utilizing the Engauge Digitizer V4.1 screenshot tool and a formula proposed by Parmar [25, 26]. The CRR, PRR, ORR, SDR were the secondary endpoints. The pooled odds ratio (OR) with 95% CI was calculated for the second point. The heterogeneity was assessed by the χ^2 -based Q-test and I² statistics. If there were statistical differences in terms of heterogeneity (I² > 50 %, p < 0.10), a random-effects model was selected [27]; otherwise, a fixed-effects model was used. The publication bias was ascertained by visually funnel plots and Egger's tests.

Results

Literature search

A total of 90 relevant publications were identified through database search and screened for relevance. After duplicating and reviewing the titles, abstracts and full texts, three articles [20, 28, 29] were eligible for this meta-analysis (Fig.1). Among these studies, one study was RCT and two studies were retrospective.

Study Characteristics

The baseline characteristics of the included publications are summarized in Table 1. Three studies including a total of 214 advanced HCC patients with PVTT included in the final analysis, 111 patients were assigned to HAIC group and 103 to the sorafenib group. Among the three studies, two were performed in Korean, and one was

performed in Japan. Based on the data available for all enrolled studies, the male to female ratio of HAIC and sorafenib group were 92/19 and 83/20, with median age was ranged from 54 years to 68 years. Most patients had Child-Pugh class A liver function in the HAIC (97.7%) and sorafenib group (83.5%), and were Vp3 and Vp4 (portal vein invasion, Vp).

Overall survival (OS)

All studies reported the median OS ranging from 4 to 14.9 months (Table 2). The HR of OS was available in all three studies. After pooling the data, no significant difference was found in the OS between HAIC and sorafenib group (HR=0.77, 95%CI: 0.56-1.06, p=0.11), although the overall meta-analysis revealed that HR was lower for the patients treated with HAIC than sorafenib. There was no heterogeneity was detected (I²= 39%, P= 0.19), so the fixed effect model was adopted (Fig. 2).

Time to progression (TTP)

Three studies provided the data of TTP with a median ranging from 1.2 to 4.4 months (Table 2). The aggregated results suggested that the risk of disease progression in the HAIC group was lower than that in the sorafenib groups (HR=0.56, 95% CI: 0.39-0.82; P=0.003) (Fig.3). We adopted the fixed effect model because no significant heterogeneity was found (P = 0.68, I² = 0%).

Partial response rate (PRR)

All three of selected studies compared the PRR between the HAIC group and Sorafenib group. No significant heterogeneity was observed in the PRR (P = 0.24, I² = 30%), so a fixed-effects model was used to pooled the data. As shown in Fig.4, the HAIC group was linked with higher PRR than sorafenib group (OR=3.31, 95% CI: 1.46-7.50; P=0.004).

Complete response rate (CRR)

All three of selected studies compared the CRR between the HAIC group and Sorafenib group. No significant heterogeneity was observed in the PRR (P = 0.91, I² = 0%), so a fixed-effects model was used to pooled the data. As shown in Fig.5, no significant difference existed in the CRR when the HAIC compared with the sorafenib group. (OR=2.54, 95% CI: 0.39-16.47; P=0.33).

Objective response rate (ORR)

All three of selected studies compared the ORR between the HAIC group and Sorafenib group. No significant heterogeneity was observed in the PRR ($P = 0.21$, $I^2 = 35\%$), so a fixed-effects model was used to pooled the data. As shown in Fig.6, the HAIC group achieved higher ORR when compared with sorafenib group ($OR=3.78$, 95% CI: 1.68-8.50; $P=0.001$).

Stable disease rate (SDR)

All studies reported the SDR data between HAIC group and sorafenib group. The pooled data showed that no significance difference was found between the two group ($OR=1.48$, 95% CI: 0.43-5.08; $P=0.001$). Random-model effect was used because high statistical heterogeneity existed ($P = 0.02$, $I^2 = 75\%$).

Discussion

Hepatocellular carcinoma is one of the leading causes of cancer-related deaths worldwide and the prognosis of HCC is very poor. Most patients were found at advanced stage is generally accompanied by PVTT and the prognosis of advanced HCC with PVTT is extremely poor. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, HCC patients with PVTT was allocated to stage C. Sorafenib is the only recommended standard therapy for HCC patients with BCLC C stage. In Asia, HAIC is another alternative treatment method for advanced HCC patients with PVTT, but the use of this treatment remains controversial. Whether HAIC can achieve a better benefit than sorafenib remains controversy. In this systematic review and meta-analysis, we examined the treatment efficacy of HAIC versus Sorafenib for advanced HCC with PVTT. Our meta-analysis showed that HAIC was significantly improved TTP, PRR, ORR in advanced HCC patients with PVTT when compared with sorafenib. Although there was no significant difference was found, the HAIC groups still improved OS, CRR, SDR. Therefore, we suggested HAIC may be a better treatment option for advanced HCC patients with PVTT than sorafenib.

Although sorafenib was recommended as the standard therapy for advanced HCC with PVTT by many guidelines[30–33], the overall survival was not satisfactory. A previous study assessed the effect of sorafenib cured the advanced HCC patients with PVTT (Vp3 and Vp4), this study reported that the median OS duration was only 3.1 months after treated with sorafenib monopoly[34]. In another study, median OS duration was only 4.3 months after sorafenib treated[35]. In the three enrolled studies, the median OS time was longer than the previous study, ranging from 4 to 7.2 months when employed sorafenib for advanced HCC with PVTT[20, 28, 29]. This difference may attribute to the difference of race and region because all the included patients were Asians. However, the median OS time varied from 7.1 to 14.9 months when treated with HAIC and all three studies reported HAIC achieved better OS than sorafenib. After pooling the data, it seemed that HAIC may lower the HR for OS than sorafenib; however, no significant difference was found between the two groups. We found that the HR for TTP in this meta-analysis was 0.56, indicating a 0.44 reduction in the risk of death in advanced HCC patients with PVTT. The result was consistent with the included three research[20, 28, 29]. The median TTP reported by the three studies ranged from 3.3 to 4.4 months in HAIC group and from 1.2 to 2.7 months in the sorafenib group. Kim GA et al[36] demonstrated that the median TTP was only 1.8 months treated with sorafenib, which was similar to the included three studies, indicating the effects of sorafenib on prolonging TTP was limited. Fujino H et al[37] reported that the TTP of advanced HCC with PVTT was 2.7 months after HAIC treated, although it shorter than the three studies, but HAIC is still ahead of sorafenib. Based on the above results, HAIC may be more recommend over sorafenib alone. In the present study, although no difference was found in CRR, SDR between the two groups. We found that HAIC significantly increases PRR, ORR by 231% and 278% for advanced patients with PVTT than the sorafenib, indicating HAIC improved the tumor response rate compared to the sorafenib. Zhuang BW et al[24] indicated that HAIC was associated with superior ORR, DCR compared with sorafenib when treated advanced cancer. Another meta-analysis also revealed that HAIC delivers a favorable result of CR, PR, ORR, however, no difference was found in SDR. The above two meta-analyses indicated that the results of this study were reliable.

Sorafenib, the only stand recommended drug for the systematic treatment of advanced HCC patients with PVTT, was reported to show benefit only approximately 30% HCC patients and acquired drug resistance was only 6 months[38]. Furthermore, Sorafenib is not widely available in many countries because of its high cost. Zhuang BW et al[24] which conducted a meta-analysis about the safety and benefits of sorafenib versus HAIC for advanced HCC, found that HAIC found that HAIC was more effective and safe than sorafenib and recommend HAIC as an alternative treatment for advanced HCC. Another meta-analysis implemented by Ni JY et al[39], compared the HAIC versus sorafenib for HCC patients with BCLC stage C; they also reported that HAIC achieved better tumor response and clinical efficacy and recommend HAIC for patients with HCC of BCLC stage C. The two previous studies were all compared HAIC with sorafenib for advanced patients(BCLC stage C). BCLC stage C was mean with vascular invasion, extrahepatic spread, Child-Pugh A or B, Performance status (PS) 1 or 2 and was defined as advanced stage disease[1]. Unlike previous two studies, our research was limited to HCC patients with PVTT which is one of the features of Barcelona stage C, maybe this was the main difference from the two previous meta-analysis and our research was more convincing.

There are several limitations should be considered in our meta-analysis. First, only one included study in our meta-analysis were RCT[20] and the other two are retrospective studies[28, 29] which may lead to selection bias. Second, two studies came from South Korea[20, 29] and one from Japan[28], which indicated regional bias, suggesting our conclusion might be applicable to Asian especially East Asians. Third, the overall sample sizes were too small to have sufficient statistical power for the efficiency of advanced HCC with PVTT between HAIC and sorafenib. So, it is necessary to conduct more randomized controlled trials with large sample size, different continents and countries to provide further clinical evidence.

Conclusion

In summary, this meta-analysis indicated demonstrated that HAIC provides better TTP, PRR, ORR than sorafenib for patients of advanced HCC with PVTT. However, no significant difference existed in OS, CRR, SDR. Therefore, we recommend HAIC as an alternative promising treatment modality for advanced HCC patients with PVTT. However, owing to the above limitations, more high-quality studies are warranted to evaluate this finding.

Abbreviations

HCC: Hepatocellular carcinoma; HAIC: Hepatic arterial infusion chemotherapy; PVTT: portal vein tumor thrombus; OS: overall survival, TTP: time to progression, PRR: partial response rate, CRR: complete response rate, ORR: objective response rate, SDR: stable disease rate. CI: confidence interval; HR: hazard ratio;

Declarations

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Hubei Chen Xiaoping Technology Development Fund (No: CXPJJH1190000-2019321)

Authors' contributions

GQOY and HLX contributed to the study conception and design. GQOY and YRW contributed to the search of the literature and acquisition of data. GDP and QL contributed to the analysis and interpretation of data. LP contributed to the drafting of the manuscript. SQL, WCL, and SL contributed to the critical revision. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Tables

Table 1 Characteristics of Three included trials in the meta-analysis

Study,Year, country	Publication type	Inclusion period	Total number	Male/female		Median age(range)		PVTT/Vp2/3/4		Child-Pugh class A/B		Etiology (HBV/Hc others)
				HAIC	Sorafenib	HAIC	Sorafenib	HAIC	Sorafenib	HAIC	Sorafenib	
				HAIC	Sorafenib	HAIC	Sorafenib	HAIC	Sorafenib	HAIC	Sorafenib	
Do Seon Song, 2014, Korean	Retro	2008-2013	110	38/12	44/16	54.3 ± 9.9	55.8 ± 9.0	7/14/29	5/16/39	45/5	47/13	44/2/3/
Michihisa Moriguchi, 2017, Japan	Retro	2002.10-2013.12	46	29/3	12/2	65 (40–81)	68/53-82	0/25/7	0/5/9	32/0	14/0	12/7/13
Jong Hwan Choi, 2018, Korean	Pro, RCT	2013.1-2015.10	58	25/4	27/2	60.3±9.5	60.2±7.3	0/10/19	0/11/18	27/2	25/4	18/5/6/1

Abbreviations: HAIC:Hepatic arterial infusion chemotherapy;PVTT: portal vein tumor thrombus, Vp: portal vein invasion, Retro: retrospective, Pro: prospective, RCT; randomized controlled trial,

Table 2. Median OS and median TTP between HAIC and Sorafenib group

Study	Median OS(months)		Median TTP(months)	
	HAIC	Sorafenib	HAIC	Sorafenib
Do Seon Song(2014)	7.1(5.4–8.8)	5.5(4.6–6.4)	3.3	2.1
Michihisa Moriguchi (2017)	10.3	4	3.6	1.2
Jong Hwan Choi(2018)	14.9(7.48–22.32)	7.2(5.43–8.97)	4.4	2.7
Abbreviations: HAIC: hepatic arterial infusion chemotherapy; OS, overall survival; TTP: Time to progression				

Figures

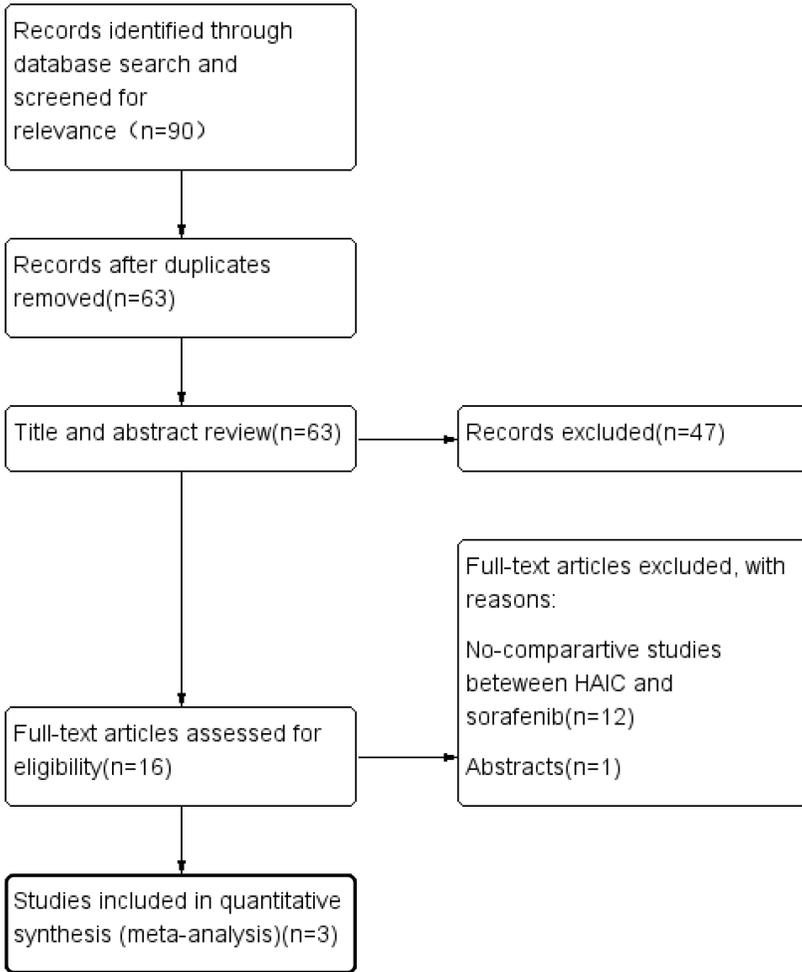


Figure 2
Flowchart of the search strategy

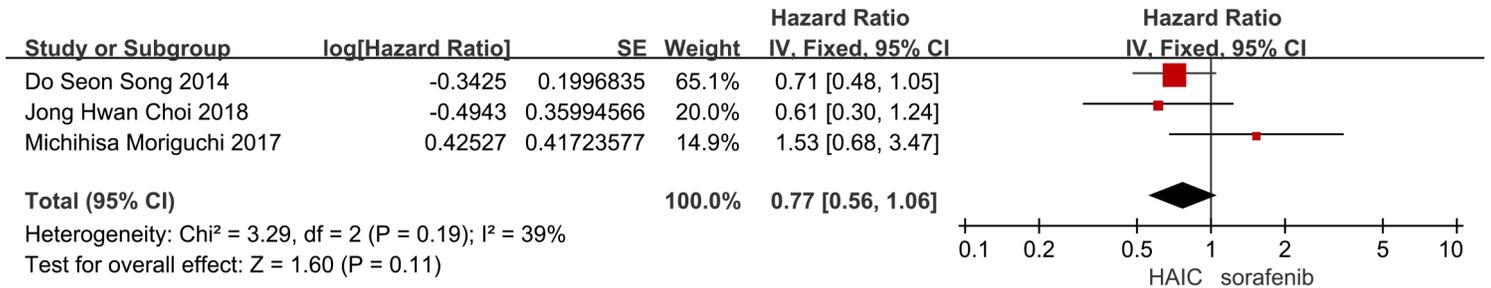


Figure 4
Overall survival between patients treated with HAIC versus sorafenib

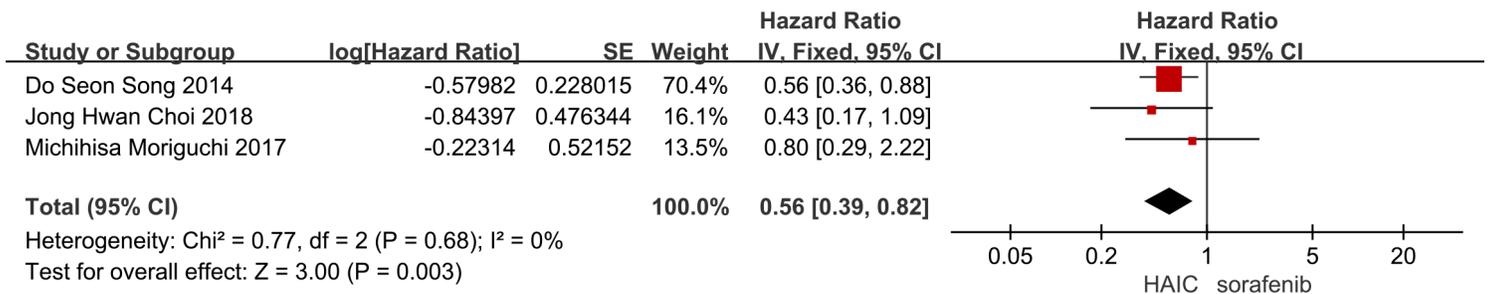


Figure 6

Time to progression between patients treated with HAIC versus sorafenib

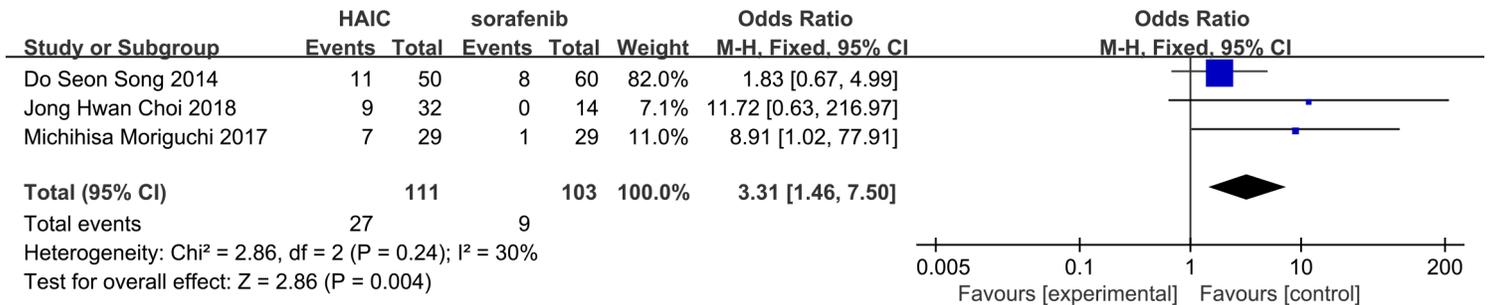


Figure 7

Partial response rate between patients treated with HAIC versus sorafenib

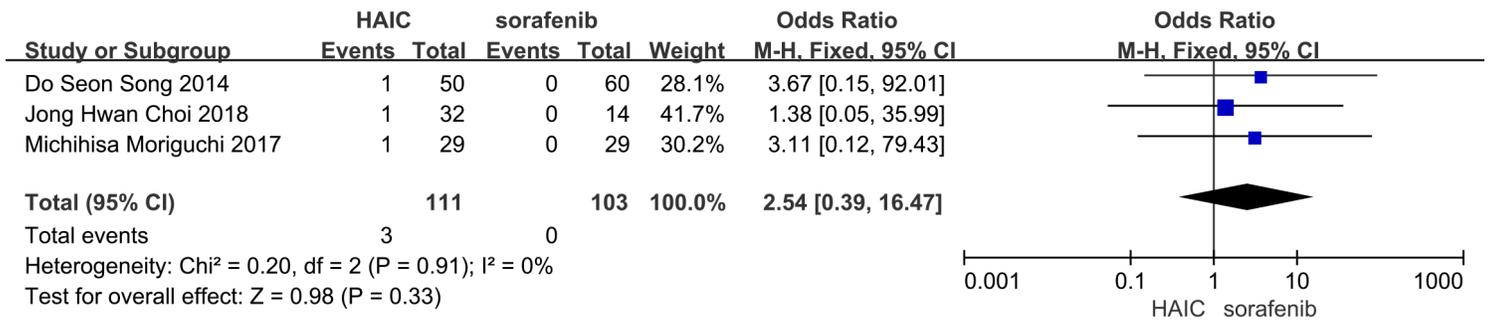


Figure 9

Complete response rate between patients treated with HAIC versus sorafenib

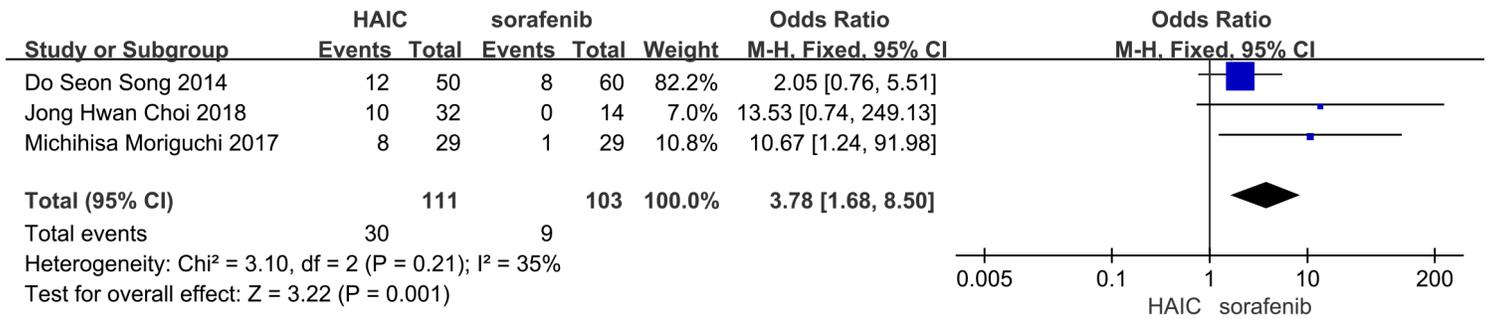


Figure 11

Objective response rate between patients treated with HAIC versus sorafenib

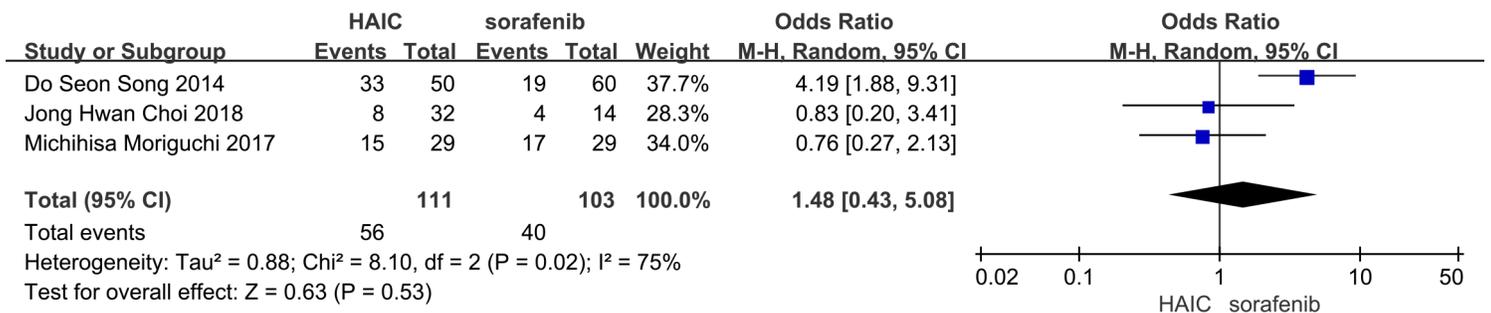


Figure 14

Stable disease rate between patients treated with HAIC versus sorafenib