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Research Article

Sorafenib-based regimens in the management of unresectable hepatocellular carcinoma: an updated meta-analysis of randomized controlled trials

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Abstract

Background: Sorafenib is the first systemic therapy approved for hepatocellular carcinoma (HCC), but its efficacy and safety for unresectable HCC remain controversial.

Methods: We searched for randomized controlled trials (RCTs) about sorafenib treatment in unresectable HCC in Web of Science, Embase, PubMed, and the Cochrane Library. Critical outcomes included overall survival (OS) and time to progression (TTP). Important outcomes included disease control rate (DCR), stable disease (SD), and partial response (PR). Hazard ratio (HR) was used to express the effect size of survival data, while dichotomous data were expressed by odds ratio (OR). Safety was measured by relative risk (RR).

Results: Six RCTs with a total of 1751 patients were included in the analysis. We found that sorafenib significantly improved the OS (HR: 0.73; 95%CI: 0.63, 0.85; P<0.001) and DCR (OR: 1.67; 95%CI: 1.14, 2.46; P<0.05) of patients with unresectable HCC, but did not significantly improve TTP. The evidence recommendation of OS and DCR results were high according to the GRADE profile. Sorafenib therapy could increase the incidence of severe drug-related adverse events, but the risk was tolerable.

Conclusion: Sorafenib treatment benefited patients with unresectable HCC in term of OS and DCR, and was comparatively safe in the management of unresectable HCC.

Abbreviations: OS: overall survival; TTSP: time to symptomatic; TTRP: time to radiologic progression; DCR: disease control rate; TTP: time to progression; PFS: progression free survival.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death among men worldwide [1]. In China, approximately 90% of HCC patients have an underlying hepatitis B virus (HBV) infection, and most patients are diagnosed with intermediate or advanced HCC according to histological diagnosis [2-4]. The Barcelona Clinic Liver Cancer (BCLC) stage system recommends treating patients with intermediate HCC with transarterial chemoembolization (TACE), and advanced HCC with sorafenib [5]. That is, these patients cannot benefit from curative treatments such as radical resection, radiofrequency ablation, and liver transplantation. Patients with advanced HCC have a 5-year survival rate of about 15-40% [6]. In 2008, Sorafenib became the first systemic therapy approved by the Food and Drug Administration (FDA) of America for advanced HCC. Sorafenib blocks the activities of the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the serine-threonine kinase Raf-1, thus inhibiting of the carcinogenesis and development of HCC [7].

The FDA's approval was based on two randomized controlled trials demonstrating that patients with advanced HCC treated with sorafenib showed better survival outcomes than those treated with placebo [8,9]. In the past several years, a large number of clinical trials have investigated the efficacy and safety of sorafenib [8-16], and several systematic reviews concluded that patients with advanced HCC could benefit from sorafenib treatment [17-20]. However, the reviews differed with regard to the pooled overall survival and time to progression. Peng et al reported that sorafenib significantly improved the overall survival and time to progression(TTP) of advanced HCC [18], while Wang et al demonstrated that TTP was significant longer in the sorafenib plus TACE group than in the TACE alone group, but differences in overall survival between the two groups did not reach significance [21]. This systematic review aims to investigate the efficacy and safety of sorafenib in the management of unresectable HCC, and uses the GRADE system to evaluate the evidence value.

Methods

Search strategy

We performed an electronic search of Web of Science, Embase, PubMed, and the Cochrane Library. (Sorafenib OR Nexavar) and (hepatic OR hepatocellular OR liver) were used as key words without time limitation. Only manuscripts published in English were included. Both abstracts, full-text and reference lists were thoroughly examined to guarantee the completeness of literature searching. The deadline of searching process was July 2016.

Inclusion criteria

Study design: phase II or III randomized controlled trials(RCTs). Patients: diagnosed with unresectable HCC (advanced HCC, HCC with metastasis or extrahepatic invasion) with perform status (PS 0-2), Child-Paugh A or B, and tolerable renal function and hematologic function who had not received any systematic therapy. Intervention: experimental group: sorafenib or sorafenib combined therapy; control group: placebo or placebo plus the same therapy as the experimental group, without sorafenib.

Exclusion criteria

Studies comparing sorafenib with other systemic drugs for HCC, studies without adequate data, phase I clinical trials, patients who received regional or systemic therapy before the trial, and patients with severe renal and hematologic dysfunction.

Quality assessment of included studies

Two investigators independently evaluated the quality of included studies according to the instructions of Cochrane Handbook for Systematic Review of Interventions [22]. Each study was assessed using the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (Figure 2).

Data extraction: Two investigators abstracted the data, collecting the following data: patients' region, number, group assigned, age, ratio of patients with Child A liver function, PS grade, Barcelona Clinic Liver Cancer(BCLC)stage, intervention, effect and safety index. Any disagreements were settled through consultation with a third investigator.

Statistics

We divided the endpoints into key outcomes and important outcomes. The key outcomes included overall survival and time to progression. The important outcomes included disease control rate, partial response rate, and stable disease. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [23]. The effect size of survival data was expressed by hazard ratio (HR), and the effect size of dichotomous data was represented by odds ratio (OR). The effect size of safety was expressed by relative risk (RR). All effect sizes were expressed as 95% confidence interval (95%CI). Heterogeneity was detected by Cochran's Q chi-square test and I^2 analysis. P-values of less than 0.1 or I^2 of more than 50% were considered to indicate heterogeneity. When heterogeneity existed, the random effect model was used to estimate the effect sizes; otherwise, the fixed model was administered. When heterogeneity was encountered, a sensitivity analysis was performed to investigate the influence of the removed study. Publication bias was measured by the Begg and Egger tests, with results presented by funnel plot. Significance was set at P<0.05. All analysis was conducted by REVMAN 5.2, and evidence recommendations and quality assessment were performed by GRADE version 3.6 [24].

Results

Study selection

The initial search yielded 859 manuscripts. After extracting duplicates, 798 manuscripts remained, of which most were deemed irrelevant based on their title or/and abstract . Of the remaining 14 studies, four were not RCTs [14,15,25,26], two compared sorafenib with chemotherapeutic drugs [16,27], and two were subgroup analysis of prior clinical trials [12,28]. Ultimately, six studies were included in our analysis [8-11,13,29] (Figure 3).

Baseline characteristics of included studies

A total of 1751 patients from Asia, Australasia, Europe, North America, Central America, and South America were enrolled in the six RCTs. Two studies compared sorafenib with placebo in the management of unresectable HCC, three studies compared the efficacy of sorafenib plus TACE with TACE alone in unresectable HCC, and sorafenib plus doxorubicin versus doxorubicin plus placebo were compared in one study. The number of subjects ranged from 62 to 602, and almost all patients presented a liver function of Child A and well performance status (PS 0-1). Two studies investigated the benefit of sorafenib in patients with BCLC B [13,29], and patients in the other four studies had BCLC B and BCLC C. Differences in the baseline characteristics did not reach significance among the enrolled studies (Table 1).

Overall survival

Five studies reported overall survival, and we did not find significant heterogeneity among them(I^2<50%, P>0.1) [8-11,29], so the fixed model was adopted for analysis. The pooled HR was 0.73(95%CI: 0.63, 0.85; P<0.001). The results demonstrated that sorafenib therapy can prolong overall survival of patients with unresectable HCC. The funnel plot detected no publication bias for this endpoint (Figure 4). We detected no publication bias in results of overall survival (Figure 5).

No of studies		Quality assessment					No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sorafenib	Control	Relative (95% CI)	Absolute		
overall survival												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.73 (0.63 to 0.84)	_1	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
time to progression												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	HR 0.81 (0.55 to 1.18)	_1	⊕⊕⊕⊕ HIGH	CRITICAL
disease control rate												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 1.67 (1.14 to 2.46)	_1	⊕⊕⊕⊕ HIGH	IMPORTANT

1 No explanation was provided

Figure 1. Evidence profile of GRADE

Table 1. Baseline characteristics of included studies

Reference	Patients' region	Number	Group	Median age	Male/female ratio(%)	Child A ratio (%)	ECOG PS(0-1) (%)	BCLC stage	Trial design	Index
[8]	Europe and Australasia 87.4%,North America 9.3%,Central and South America 4.3%	602	Sorafenib 299, placebo 303	T: 64.9, C: 66.3	T(87:13) C(87:13)	T:95% C:98%	T:92% C:93%	B:106 C:496	Sorafenib 400mg bid vs placebo bid	Primary end points: OS, TTSP. secondary end points:TTRP, RR,DCR, safety
[10]	59.3%North America, 34.3%Europe, 2%Asia, 4.4%South America	96	Doxorubicin+ sorafenib 47 vs doxorubicin + placebo 49	T:66 C: 65	T(66:34), C(85.7:14.3)	T:100, C::95.9	T:85.1, C:83.7	NR	Doxorubicin every 21 days plus sorafenib 400mg bid vs doxorubicinplus placebo bid	TTP, OS, PFS, response rate ,safety
[11]	Asia 100%	458	TACE+sorafenib 229 vs TACE+placebo 229	T:69 C:70	T(76:24) C(73:27)	T:100 C:100	T:100 C:100	NR	After TACE, soarafenib 400mg bid vs placebo bid daily	Primary end point: TTP secondary end point :OS, safety
[9]	Asia	226	Sorafenib 150 Placebo 76	T:51 C:52	T(84.7:15.3) C(66:34)	T:97.3 C:97.4	T:94.7 C:96	B:10 C:216	Sorafenib 400mg bid vs placebo bid	OS,TTP,TTSP,RR, safety
[13]	Europe	62	TACE+Sorafenib:31 TACE+placebo:31	T:73 C:72.8	T(58:42) C(61:39)	T:100 C:100	T:100 C:100	B:62	After TACE, Sorafenib 400mg bid vs placebo	TTP, safety
[2,9]	Europe, Asia, and North America	307	Sorafenib+TACE:154 Placebo+TACE:153	T:64.5 C:63.0	T(87.7:12.3) C(82.4:17.6)	T:100 C:100	T:100 C:100	B:307	Sorafenib 400mg bid+ TACE vs placebo+ TACE	TTP,OS, DCR, safety

Figure 2. Risk of bias summary

Time to progression

Six studies provided data on time to progression [8-1113,29]. We found significant heterogeneity among the studies (I^2=89%, P<0.1), so a random model was used for effect size measurement. The pooled HR was 0.81 (95%CI: 0.55, 1.18; P>0.05). We found that sorafenib therapy did not benefit patients with unresectable HCC in terms of time to progression. Subsequently, we removed the study by Sansonno *et al.* [13], and a heterogeneity test of the remaining five studies yielded I^2=58%, P=0.05<0.1. The pooled HR of these five studies was 0.67 (95%CI: 0.54, 0.83; P<0.05) (Figure 6)

Disease control rate

Three studies reported the disease control rate [8,9,29]. Heterogeneity was not significant among these three studies (I^2=49%, P>0.1). The pooled OR was 1.67 (95%CI: 1.14, 2.46; P<0.05), indicating that sorafenib therapy could improve tumor response in patients with unresectable HCC (Figure 7)

Partial response

Three studies published data on partial response [8,9,29]. No significant heterogeneity was found among these studies. A test for overall effect showed that the OR was 1.57 (95%CI: 0.95, 2.61; P>0.05). We found that sorafenib treatment did not increase partial response in patients with unresectable HCC (Figure 8).

Quality of evidence

According to the GRADE profile, evidence is divided into important and critical. The quality of evidence is ranked as high, moderate, low, and extremely low. Based on the instructions of the GRADE system, the result of our OS, TTP, DCR, and PR analysis was recommended as high quality evidence, see details in the following evidence profile of GRADE (Figure 1).
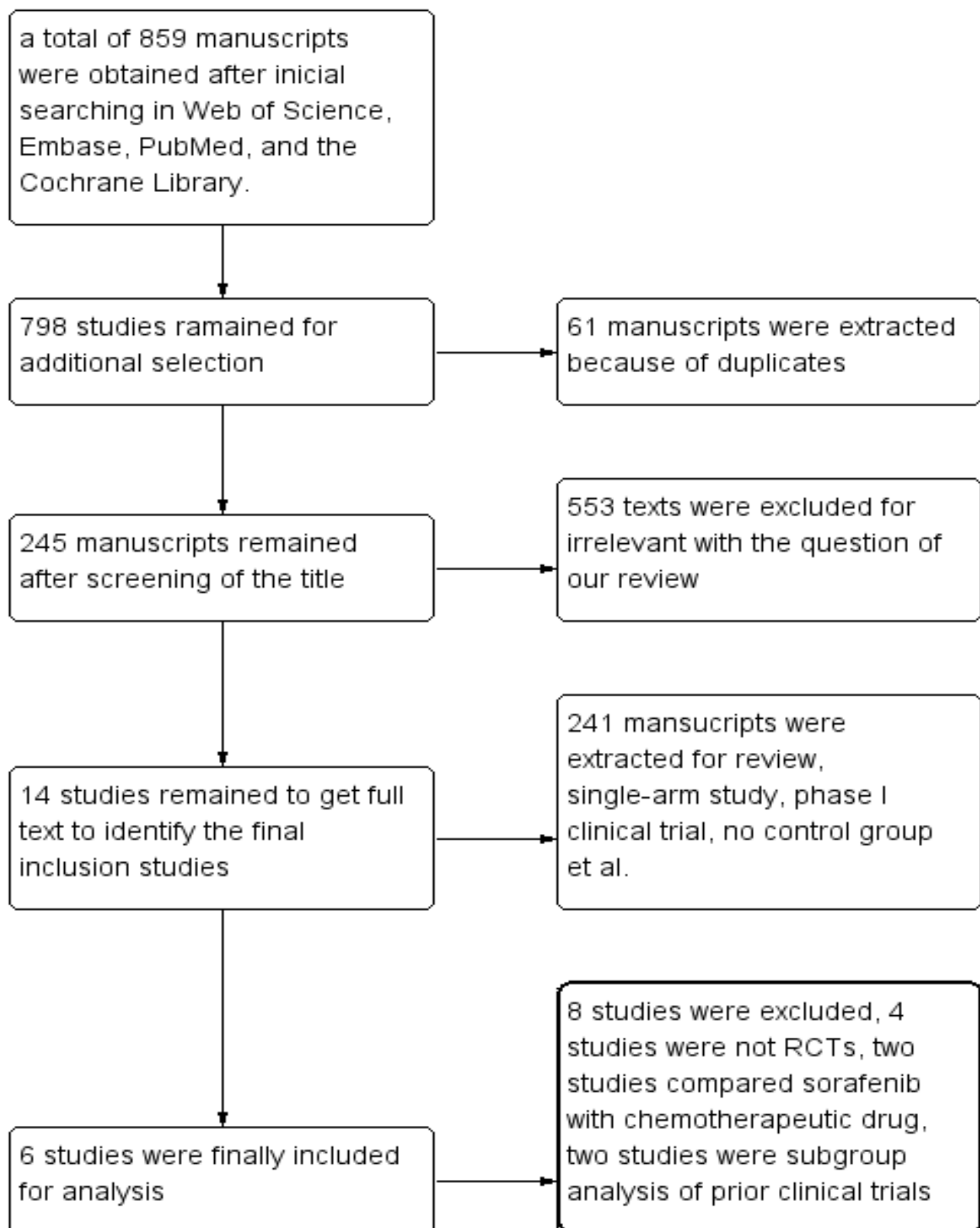
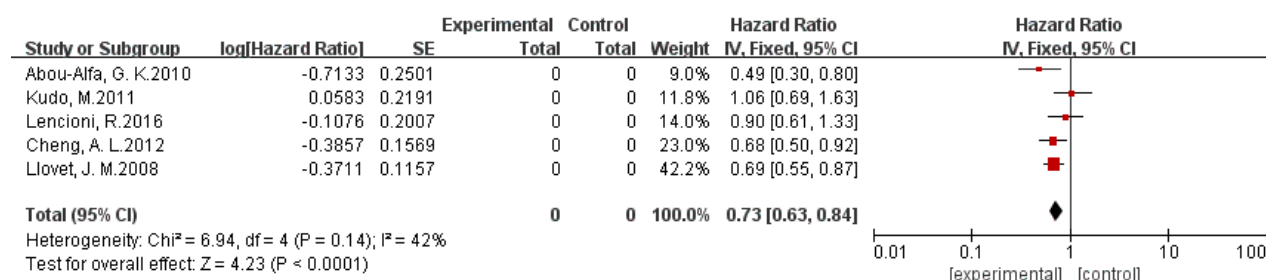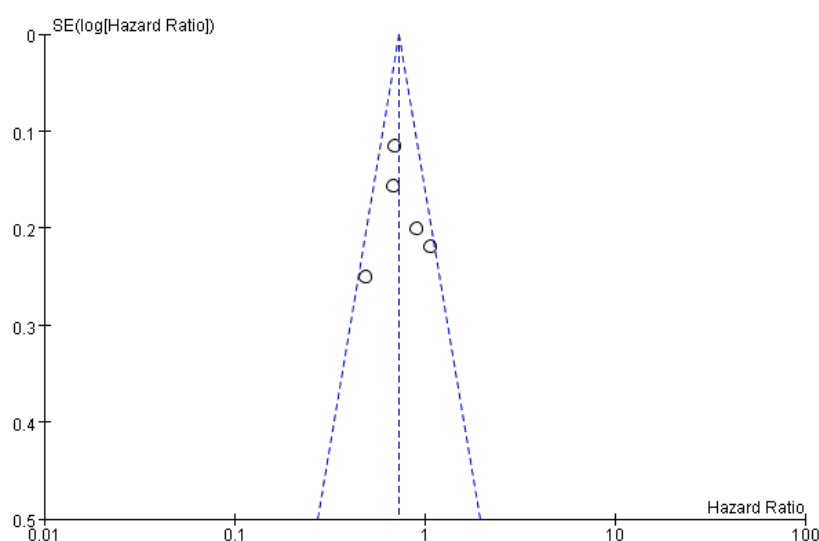**Figure 3. Flow gram of study selection**

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Abou-Alfa, G. K.2010	-0.7133	0.2501	0	0	9.0%	0.49 [0.30, 0.80]
Kudo, M.2011	0.0583	0.2191	0	0	11.8%	1.06 [0.69, 1.63]
Lencioni, R.2016	-0.1076	0.2007	0	0	14.0%	0.90 [0.61, 1.33]
Cheng, A. L.2012	-0.3857	0.1569	0	0	23.0%	0.68 [0.50, 0.92]
Llovet, J. M.2008	-0.3711	0.1157	0	0	42.2%	0.69 [0.55, 0.87]
Total (95% CI)			0	0	100.0%	0.73 [0.63, 0.84]

Heterogeneity: Chi² = 6.94, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 4.23 (P < 0.0001)

Figure 4. Analysis of overall survival

Figure 5. Detection of publication bias

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
Abou-Alfa, G. K.2010	-0.6931	0.2606	0	0	14.3%	0.50 [0.30, 0.83]
Cheng, A. L.2012	-0.5621	0.1665	0	0	16.9%	0.57 [0.41, 0.79]
Kudo, M.2011	-0.1393	0.115	0	0	18.1%	0.87 [0.69, 1.09]
Lencioni, R.2016	-0.2269	0.155	0	0	17.2%	0.80 [0.59, 1.08]
Llovet, J. M.2008	-0.5447	0.1295	0	0	17.8%	0.58 [0.45, 0.75]
Sansonno, D.2012	0.9163	0.2089	0	0	15.8%	2.50 [1.66, 3.76]
Total (95% CI)			0	0	100.0%	0.81 [0.55, 1.18]

Heterogeneity: Tau² = 0.19; Chi² = 43.70, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.09 (P = 0.28)

Figure 6. Analysis of time to progression

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cheng, A. L.2012	53	150	12	76	10.8%	2.91 [1.44, 5.88]
Lencioni, R.2016	107	154	99	153	31.8%	1.24 [0.77, 2.00]
Llovet, J. M.2008	129	299	97	303	57.4%	1.61 [1.16, 2.25]
Total (95% CI)		603		532	100.0%	1.63 [1.27, 2.10]
Total events	289		208			

Heterogeneity: Chi² = 3.89, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 3.82 (P = 0.0001)

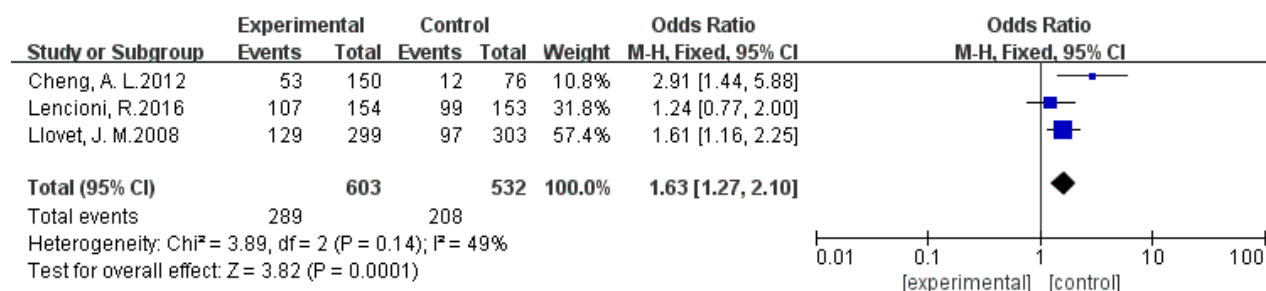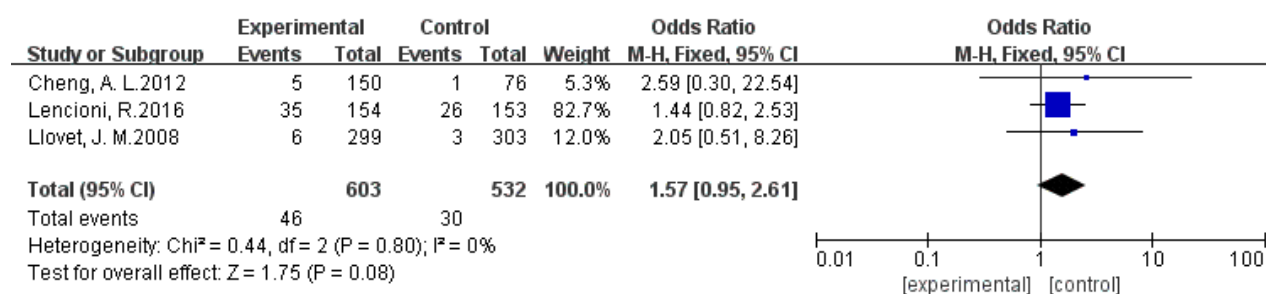**Figure 7. Analysis of disease control rate**

Figure 8. Analysis of partial response

Adverse events

The most common adverse events of sorafenib therapy were hand-foot skin reaction (HFSR), fatigue, rash, hypertension, and diarrhea. All six studies reported information on adverse events, and investigators generally divided adverse events into all-grade and severe adverse events (grade 3 and 4) according to the National Cancer Institute's Common Terminology Criteria for adverse events [30]. The RRs of HFSR, rash, hypertension, and diarrhea were 20.12(95%CI: 9.18, 44.08; $P<0.05$), 8.62(95%CI: 2.43, 30.60; $P<0.05$), 3.57(95%CI: 1.05, 12.04; $P<0.05$), and 4.06(95%CI: 2.27, 7.27; $P<0.05$), respectively. Therefore, administration of sorafenib could significantly increase the incidence of drug-related adverse events in patients with unresectable HCC.

Discussion

This systematic review investigates the efficacy and safety of sorafenib for patients with unresectable HCC. We demonstrate that sorafenib therapy improves overall survival and increases the disease control rate for these patients. However, it did not lead to a significant difference in time to progression, partial response, or stable disease compared with control groups. In addition, sorafenib treatment significantly increased the incidence of HFSR, rash, hypertension, and diarrhea in patients with unresectable HCC.

Previous meta-analyses have obtained results consistent with those of the present study. Peng et al demonstrated that sorafenib improved overall survival (HR: 0.74) in patients with advanced HCC. They also found a time to progression benefit of sorafenib therapy (HR: 0.69; $P<0.05$), which was inconsistent with our finding (HR:0.81; $P>0.05$) [18]. That study included seven RCTs with a total of 3807 patients, of which, two clinical trials compared the efficacy of sorafenib with other systemic drugs [16,27], decreasing the reliability of the findings. In the present review, when we removed the study by Sansonno [13], time to progression in the sorafenib therapy group was significantly longer than that of the control group(HR:0.67;95%CI: 0.54, 0.83; $P<0.05$). The sample size of the Sansonno study was relatively small, which might have led to selection bias in the results. Moreover, etiology was more heterogeneous in this study compared with the other five studies. Patients with underlying hepatitis C virus (HCV) induced BCLC B HCC were included in the trial, and investigators found that sorafenib plus TACE provided superior benefit for patients with BCLC B HCC in terms of time to progression. Previous studies demonstrated that HCC patients with underlying HCV infection had higher long-term recurrence and multi-center progression [31]. Sorafenib may delay tumor progression by suppressing both tumor growth and neoangiogenesis, and decreasing the rate of metachronous multi-center progression [31]. Thus, the HR of time to progression (HR=2.5) was higher in the Sansonno study than that in the other five studies.

Three prior systematic reviews compared the effect of sorafenib plus TACE with TACE alone in patients with advanced HCC [17,20,21]. They all found that sorafenib combined with TACE significantly prolonged the time to progression, but did not significantly improve overall survival in patients with advanced HCC, which was inconsistent with our findings. As we know, sorafenib decreases short and long term recurrence and tumor progression, and time to progression is an index influenced by multiple tumor progression and metachronous [32,33]. In addition, TACE is regarded as a regional therapy recommended for patients with intermediate HCC, which can induce satisfactory tumor necrosis when the diameter <5 cm; embolism could decrease the blood supply to the target tumor, further slowing the disease progression [34]. Thus, patients with sorafenib combined with TACE therapy may have a superior benefit in time to progression than those with TACE or sorafenib alone.

The incidence of severe drug-related adverse events was higher in the sorafenib treatment group than in the control group, which was consistent with the findings of previous reviews. The most common drug-related adverse events of sorafenib are HFSR, rash, diarrhea, hypertension, and fatigue. Other rare severe adverse events were reported in previous studies, but in our review, none of the six included studies reported fatal adverse events. Previous reviews even suggested that early dermatologic adverse events predicted better survival of patients treated with sorafenib [35]; however, more studies are needed to reach a conclusion. Our review demonstrated that sorafenib treatment could raise the incidence of adverse events, but that risk is fairly tolerable. In clinical practice, investigators have proposed measures to mitigate these events, which could increase the safety of sorafenib management [36].

Our study has some limitations. First, the number of enrolled patients was somewhat small, so while the included studies were all RCTs, the number of subjects decreases the reliability of the final conclusion. Second, disease etiology, age, BCLC stage, and PS grade are all prognostic factors for unresectable HCC, but we did not perform subgroup analysis to explore the influence of these factors in sorafenib treatment.

We conclude that sorafenib can benefit patients with unresectable HCC in overall survival and disease control , which increasing the incidence of drug-related adverse events, which are comparatively tolerable. The future frontier may lie in the investigation of sorafenib for management of intermediate HCC, but more RCTs with large sample size are needed to explore sorafenib for the management of unresectable HCC.

Author contributions

Xu MQ designed the review; Yi PS wrote the paper; Xu LL discussed the theme presented in article, Zhang M and Xu MQ revised the draft. Peng Sheng Yi and Min Huang contributed equally to this work.

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