Hepatol Int (2016) 10:501–510
DOI 10.1007/s12072-015-9700-7

ORIGINAL ARTICLE

Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review

Guiliang Wang[1,2] · Yan Liu[2] · Shu-feng Zhou[3] · Ping Qiu[1] · Linfang Xu[1] · Ping Wen[1] · Jianbo Wen[1] · Xianzhong Xiao[4]

Received: 19 May 2015 / Accepted: 25 December 2015 / Published online: 8 February 2016

Abstract
Purpose Combination therapy of sorafenib and transarterial chemoembolization (TACE) has shown benefits in treating advanced hepatocellular carcinoma (HCC). This study evaluated the efficacy and safety of TACE + sorafenib.
Methods MEDLINE, the Cochrane Library, EMBASE, and the ISI Web of Knowledge were searched (until 31 December 2013) for studies comparing TACE and TACE + sorafenib in treating patients with advanced HCC. Sensitivity and quality assessments were performed.
Results Five comparative studies (2 were randomized control trials) that included 899 patients were used in the meta-analysis. Patients treated with TACE + sorafenib had better prognoses in terms of time to progression (TTP) compared to those with TACE + placebo or TACE alone; hazard ratios (HRs) ranged from 0.40 to 0.87, with the combined HR 0.61 (95 % CI 0.39–0.95, $p = 0.031$). However, the combined HR for overall survival (OS) did not differ significantly between patients treated with TACE + sorafenib and those with TACE + placebo or TACE alone (combined HR = 0.79, 95 % CI = 0.54–1.16, $p = 0.235$). Sensitivity analysis indicated the findings for TTP may be overly influenced by at least one of the studies.
Conclusions In summary, our meta-analysis found that TACE + sorafenib can improve TTP. We did not find the combined therapy improved OS. Additional randomized controlled studies are necessary to further investigate the clinical benefit of TACE + sorafenib in treating advanced HCC.

Keywords Combined modality therapy · Liver neoplasms · Meta-analysis · Sorafenib · Systematic review · Therapeutic chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is one of the most common forms of cancer worldwide and is particularly present in some Asian countries due to the high prevalence of hepatitis B virus infection [1, 2]. Approximately 30 % of patients present with advanced or unresectable HCC, and consequently the mortality rate for HCC is high [3, 4].

Due to the high rates of advanced disease, palliative treatment, aimed at increasing the length of survival after diagnosis, is a very important component of managing HCC [5]. A number of therapies are used to treat advanced HCC such as transarterial chemoembolization (TACE), radiation, systematic chemotherapy, portal vein stent, surgical resection, percutaneous ethanol injection, I-125 implantation, laser ablation, and conservative treatment [6–12]. Currently, there is no consensus regarding a common treatment strategy for patients with advanced HCC [13].

✉ Xianzhong Xiao
xianzhongxiaoxxz@sina.com

[1] Department of Digestive Internal Medicine, Gan Nan Medical University Pingxiang Hospital, 128 Guangchang Road, Pingxiang 337055, Jiangxi, People's Republic of China

[2] Department of Digestive Internal Medicine, 307 Hospital of PLA, Beijing, People's Republic of China

[3] Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, Tampa, FL 33612, USA

[4] Laboratory of Shock, Department of Pathophysiology, Xiangya School of Medicine, Central South University, Changsha, Hunan 410008, People's Republic of China

TACE, which delivers chemotherapy to the tumor location, is considered the standard treatment for unresectable HCC and has been demonstrated to provide a modest survival benefit [14, 15]. However, failure of TACE therapy is common, and studies have found that this may, in part, result from cellular adaptation to hypoxia resulting from the chemotherapy by neoangiogenesis [16]. Vascular endothelial growth factor (VEGF) plays an important role in promoting neoangiogenesis [16–18]. Sorafenib, an antiangiogenic drug that inhibits the VEGF signaling pathway, is indicated for the treatment of patients with unresectable HCC [19].

The use of sorafenib with TACE in treating advanced HCC has been actively studied, although the findings have been inconsistent [20]. Hence, the effectiveness of the combined use of sorafenib and TACE in HCC, especially in the majority of patients with more advanced disease, is not well understood. This systematic review and meta-analysis aimed to analyze the safety and efficacy of sorafenib combined with TACE in treating unresectable HCC.

Materials and methods

Search strategy

This meta-analysis was conducted in accordance with the PRISMA guidelines [21]. MEDLINE, the Cochrane Library, EMBASE, and the ISI Web of Knowledge were searched (until 31 December 2013) using combinations of the following keywords: hepatocellular carcinoma/HCC/hepatoma, sorafenib and chemoembolization transarterial chemoembolization/TACE. Randomized controlled trial studies that evaluated patients who had diagnoses of HCC and received treatment with sorafenib combined with TACE were included. The included studies provided numerical information about the specified primary or secondary outcomes (see below). Studies not published in English were excluded. Letters, commentaries, editorials, and case reports were also excluded. Potential studies were reviewed by two independent reviewers, and a third reviewer was consulted if there was uncertainty regarding eligibility.

Data extraction

The following information was extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, patient demographics, key clinical characteristics (tumor stage, performance status, rate of viral hepatitis infection, chemoembolization treatment regimen), survival outcomes, tumor responses, and adverse events. Two independent reviewers extracted the data, and a third reviewer was used to solve any discrepancies.

Quality assessment

The Delphi list was used to assess the quality of the randomized controlled trials [22]. The Newcastle-Ottawa scale was used to assess the quality of the nonrandomized controlled study [23].

Statistical analysis

The primary outcome measure was time to progression (TTP), and the secondary outcomes measures were overall survival (OS) and adverse events.

The hazard ratio (HR) with 95 % confidence interval (CI) was calculated for TTP and OS among patients treated with TACE + sorafenib compared to those with TACE + placebo or TACE only. Because adverse events are rare, the Peto odds ratio (OR) with 95 % CI was calculated for the adverse event outcomes [22]. An HR/OR <1 indicated TACE + sorafenib was favored. Because the number of studies included in the meta-analysis was small, the heterogeneity tests may have had low statistical power [23]. Tests for heterogeneity are often underpowered, and random-effects models are routinely used [24]. The National Research Council report recommends the use of random-effects approaches for meta-analysis and the exploration of sources of variation in study results [25]. Combined HRs were calculated, and a two-sided p value <0.05 was considered to indicate statistical significance. Sensitivity analysis was performed for primary outcomes based on the leave-one-out approach. All statistical analyses were performed using the Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

We did not evaluate publication bias as the number of studies included in the meta-analysis was too small to assess for publication bias using a funnel plot [26].

Results

Literature search

After the initial search and removal of duplicates, a total of 96 articles were identified for screening (Fig. 1). Of these, 75 were subsequently excluded for not being relevant. Ten additional studies were eliminated because the intervention studied did not involve TACE ($n = 9$) or only reported a study protocol ($n = 1$). Five studies were included in the systematic review [26–31].

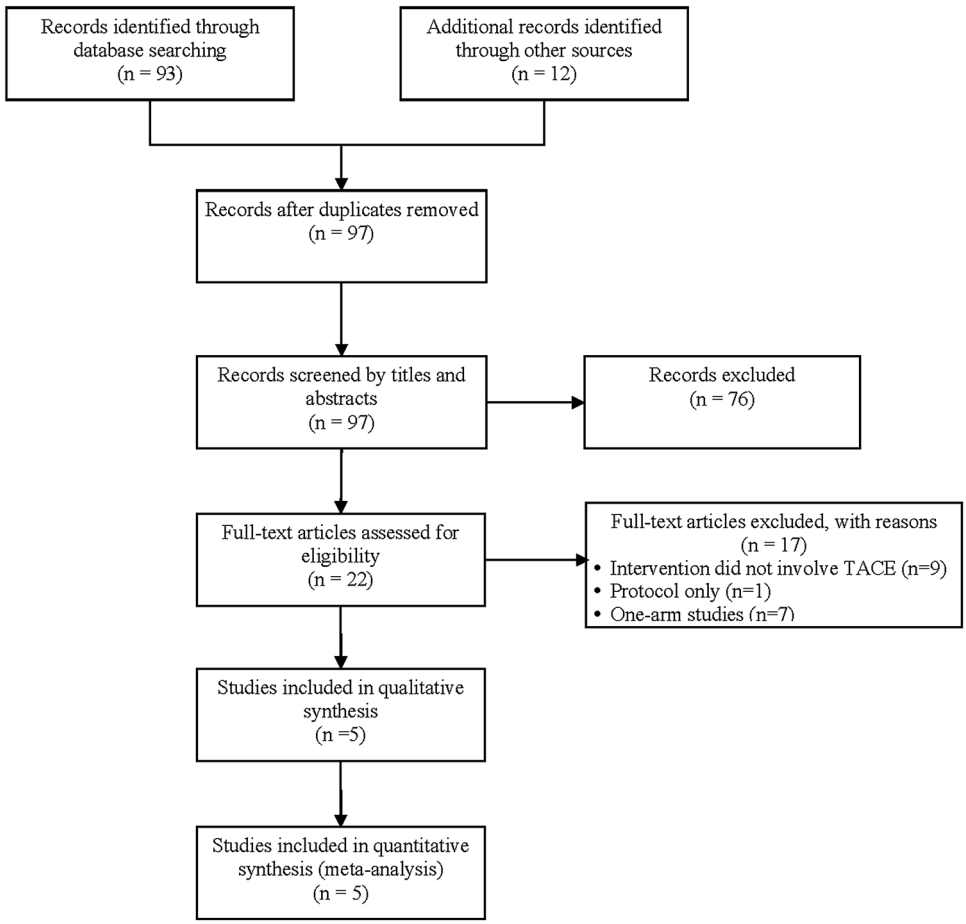

Fig. 1 Flowchart of study selection

Study characteristics

The 5 studies included 899 patients with unresectable HCC, with 400 patients treated with TACE + sorafenib and 499 treated with TACE + placebo or TACE alone. The four studies in the meta-analysis [27, 28, 29, 31] included 809 patients ($n = 355$ for sorafenib + TACE and $n = 454$ for TACE + placebo or TACE alone). The total number of patients in each of the 5 studies ranged from 43 to 458. The mean age across the studies ranged from 49 to 73 years, and most patients were male (Table 1). For both treatment groups, the most common BCLC stages were B (intermediated stage) and C (advanced stage); most patients had a Child-Pugh class A tumor and ECOG score of 0–1 (Table 1). The chemobolization and dose of sorafenib varied across the studies (Table 2).

The median TTP time ranged from 5.4 to 9.2 and 3.7 to 4.9 months for patients with TACE + sorafenib and those with TACE + placebo or TACE alone, respectively. The median OS time ranged from 7.5 to 29.7 and 5.1 to 18.3 months for patients with TACE + sorafenib and those with TACE + placebo or TACE alone, respectively.

Safety

Meta-analysis

Time to progression—primary outcome The study of Qu et al. [26] was excluded from the meta-analysis of TTP because it did not provide point estimates and 95 % CIs for HR regarding TTP; hence, three [27, 29, 31] studies were used for the meta-analysis. Because of the small number of studies included, a random-effects model was used. Patients treated with TACE + sorafenib had better prognoses in terms of TTP compared to those with TACE + placebo or TACE alone; HRs ranged from 0.40 to 0.87, with the combined HR = 0.61 (95 % CI 0.39–0.95, $p = 0.031$) (Fig. 2).

Overall survival—secondary outcome Only three [27, 29, 31] of the four studies provided the point estimate (HR) and 95 % CI for OS. The combined HR revealed that the OS did not significantly differ between patients treated with TACE + sorafenib and those with TACE + placebo or TACE alone (combined HR 0.79, 95 % CI 0.54–1.16, $p = 0.235$) (Fig. 3).

Table 1 Characteristics of included studies in the meta-analysis and systematic review

References	Study design	Treatment	Number of cases	Mean age (years)	Male (%)	BCLC stage (%)	Child-Pugh (%)	ECOG (%)	Viral hepatitis (%)	Quality scores*
Bai et al. [29]	Prospective non-randomized	TACE + sorafenib vs. TACE alone	82 vs. 164	54 vs. 52	89 vs. 89	B (23.2), C (76.8) vs. B (27.4), C (72.6)	A (76.8),B (23.1) vs. A (70.1), B (29.9)	Score 0 (36.6), Score 1 (46.4), Score 2 (14.6), Score 3 (1.2), Score 4 (1.2) vs. Score 0 (29.3), Score 1 (61.6), Score 2 (9.1)	HBV (87.8), HCV (4.9) vs. HBV (89.6), HCV (4.3)	9
Muhammad et al. [30]	Retrospective cohort study	TACE + sorafenib vs. TACE alone	13 vs. 30	61 vs. 59	100 vs. 100	A (46.2), B (15.4), C (38.5) vs. A (73.3), B (26.7)	A (84.6), B (15.4) vs. A (76.7), B (23.3)	NA	HCV (46.1) vs. HCV (56.6)	6
Sansonno et al. [28]	RCT	TACE + sorafenib vs. TACE + Placebo	31 vs. 31	73 vs. 72.8	58.1 vs. 61.3	All B (100)	All A (100)	Score 0 (76), Score 1 (24) vs. Score 0 (77), Score 1 (23)	All HCV (100)	7
Qu et al. [26]	Retrospective study	TACE + sorafenib vs. TACE alone	45 vs. 45	51 vs. 49	91.1 vs. 91.1	B (35.6), C (64.4) vs. B (37.8), C (62.2)	A (73.3), B (26.7) vs. A (77.8), B (22.2)	Score 0 (95.6), Score 1 (4.4) vs. Score 0 (91.1), Score 1 (8.9)	HBV (84.4) vs. HBV (82.2)	6
Kudo et al. [27]	RCT, Phase III	TACE + sorafenib vs. TACE + Placebo	229 vs. 229	Median: 69 vs. 70	76 vs. 73.4	NA	All A (100)	Score 0 (87.8), Score 1 (12.2) vs. Score 0 (88), Score 1 (12)	HBV (20.5), HCV (60.7) vs. HBV (21.1), HCV (62.7)	8

BCLC Barcelona Clinic Liver Cancer Classification, *ECOG* Eastern Cooperative Oncology Group, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NA* not available, *NE* could not estimate, *RCT* randomized controlled trial, *TACE* transcatheter arterial chemoembolization

* The Delphi list was used to assess the quality of randomized controlled trials. The Newcastle-Ottawa scale was used to assess the quality of nonrandomized controlled study

Table 2 Summary of study participants and study outcomes

References	Treatment	Number of cases	Chemoembolization	Dose of sorafenib	Median treatment period of sorafenib	Tumor response, %	Median TTP (months)	Median OS (months)
Bai et al. [29]	TACE + sorafenib vs. TACE alone	82 vs. 164	Mitomycin, doxorubicin	400 mg twice daily	NA	CR (0), PR (9.7), SD (48.8), PD (41.5) vs. CR (0), PR (3.4), SD (41.1), PD (55.5)	6.3 vs. 4.3	7.5 vs. 5.1
Muhammad et al. [30]	TACE + sorafenib vs. TACE alone	13 vs. 30	Doxorubicin	200 mg twice daily then increased to 400 mg twice daily	NA	NA	NA	20.8 vs. 18.3
Sansonno et al. [28]	TACE + sorafenib vs. TACE + Placebo	31 vs. 31	Mitomycin, doxorubicin	400 mg twice daily	NA	NA	9.2 vs. 4.9	NA
Qu et al. [26]	TACE + sorafenib vs. TACE alone	45 vs. 45	Oxaliplatin, fluorouracil, epirubicin	400 mg twice daily	11.61 months vs. NA	NA	NA	27 vs. 17
Kudo et al. [27]	TACE + sorafenib vs. TACE + Placebo	229 vs. 229	Epirubicin, cisplatin, doxorubicin, mitomycin	200 mg twice daily	17.1 vs. 20.1 weeks	NA	5.4 vs. 3.7	29.7 vs. NE

CR complete response, *NA* not available, *NE* not estimable because of immaturity of data, *PD* progressive disease, *PR* partial response, *SD* stable disease, *TACE* transcatheter arterial chemoembolization

Adverse effects—secondary outcome The summary of adverse events is shown in Table 3. We classified the adverse events according to Common Terminology Criteria for Adverse Events (version 4.03) [32]. The most frequent adverse events across the studies associated with TACE + sorafenib treatment were hand-foot skin reactions, diarrhea and hypertension). The individual and overall adverse events for the included studies are presented in a Forest plot in Fig. 4. Random-effects models for rates of hand-foot skin reaction, diarrhea and hypertension were used. Patients treated with TACE + sorafenib had a higher frequency of hand-foot skin reactions, diarrhea and hypertension compared to those with TACE + placebo or TACE alone (all $p < 0.05$).

Sensitivity analysis We performed sensitivity analyses for TTP, OS, and rates of adverse events in which the data analyzed after each study was removed in turn (Table 4). Removal of the study of Sansonno et al. [28] or Bai et al. [29] caused the pooled HR for TTP to become nonsignificant. These findings suggest that these two studies overly impacted the combined findings. For OS, the results differed when Kudo et al. [27] was removed; the pooled HR for OS became significant, suggesting this study may have overly influenced the findings. For rates of diarrhea and hypertension, the results differed when Kudo et al. [27] was removed; the pooled Peto OR became nonsignificant, suggesting this study may have overly influenced the findings. However, the magnitude of the combined estimate for hand-foot skin reactions did not vary markedly with the removal of the studies, indicating these findings are robust.

Quality assessment of studies with two treatment arms The quality of the data was evaluated for the two included studies that were randomized control trials using the Delphi list [27, 28]. The study of Kudo et al. [27] received 8 points and of Sansonno et al. [28] 7 points, indicating the data were of good quality. A risk for detection bias was present because the outcome assessors in both studies were not blinded. The Sansonno et al. [28] study also did not include an intention-to-treat analysis. The quality of the Bai et al. [29], Muhammad et al. [30] and Qu et al. [26] studies, which were non-randomized, was evaluated using the

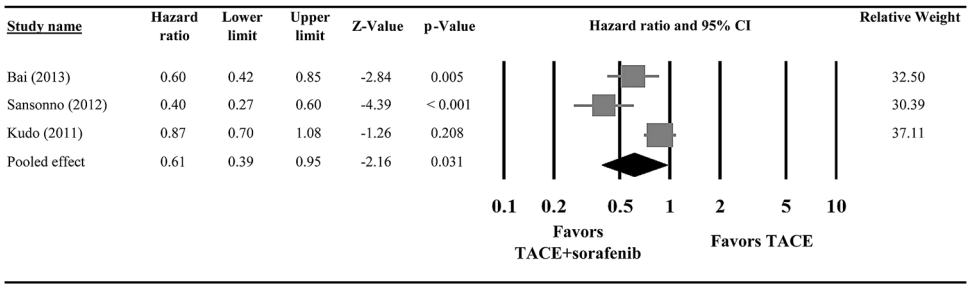

Fig. 2 Meta-analysis for treatment effects of sorafenib in combination with TACE on progression-free survival in patients with unresectable hepatocellular carcinoma

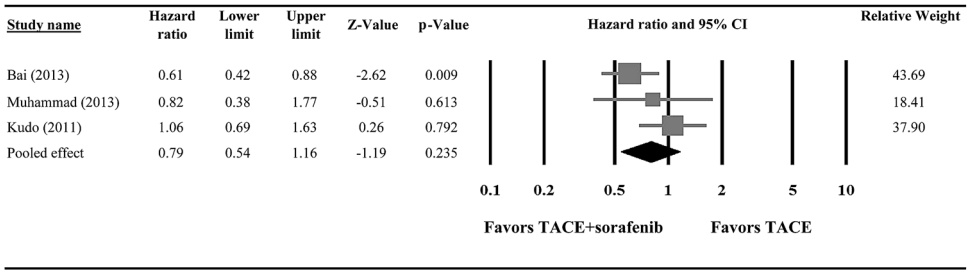

Fig. 3 Meta-analysis for treatment effects of sorafenib in combination with TACE on overall survival in patients with unresectable hepatocellular carcinoma

Table 3 Summary of adverse events

1st AU (year)		Bai et al. [29]	Muhammad et al. [30]	Sansonno et al. [28]	Qu et al. [26]	Kudo et al. [27]
No. for safety set (*n*)		82 vs. 164	13 vs. 30	40 vs. 40	45 vs. 45	229 vs. 229
Category	Adverse events (%)					
Skin and subcutaneous tissue disorders	Hand-foot skin reaction	63.4 vs. 0	15.4 vs. 0	10 vs. 0	82	82 vs. 7
	Alopecia	45.1 vs. 0	–	0 vs. 0	–	41 vs. 3
	Rash/desquamation	–	–	20 vs. 2.5	58	40 vs. 11
Gastrointestinal disorders	Diarrhea	36.6 vs. 0	7.7 vs. 0	10 vs. 7.5	48.9	31 vs. 5
	Nausea	–	0 vs. 10	17.5 vs. 7.5	26.7	–
	Abdominal pain	–	7.7 vs. 20	–	–	–
Investigations	Elevated AST	–	15.4 vs. 3.3	–	–	25 vs. 5
	Elevated ALT	–	–	–	–	21 vs. 5
	Elevated amylase	–	–	–	–	21 vs. 8
	Elevated lipase	–	–	–	–	44 vs. 8
General disorders and administration site conditions	Fatigue	24.4 vs. 0	–	22.5 vs. 7.5	55.6	–
Metabolism and nutrition disorders	Anorexia	–	–	7.5 vs. 10	31.1	–
	Hypophosphatemia	–	–	–	–	28 vs. 6
	Other metabolic abnormality	–	–	–	–	32 vs. 4
Vascular disorders	Hypertension	8.5 vs. 0	7.7 vs. 0	15.3 vs. 10	55.6	31 vs. 7

The blank indicated no reported events

Newcastle-Ottawa scale. The Bai et al. data were considered of high quality as they received a score of 9. Muhammad et al. and Qu et al. received a score of 6 because they may have had selection bias as they did not explain the selection of participants.

Discussion

This meta-analysis evaluated the efficacy of TACE alone or TACE + sorafenib in treating patients with advanced HCC. We found that the addition of sorafenib to TACE

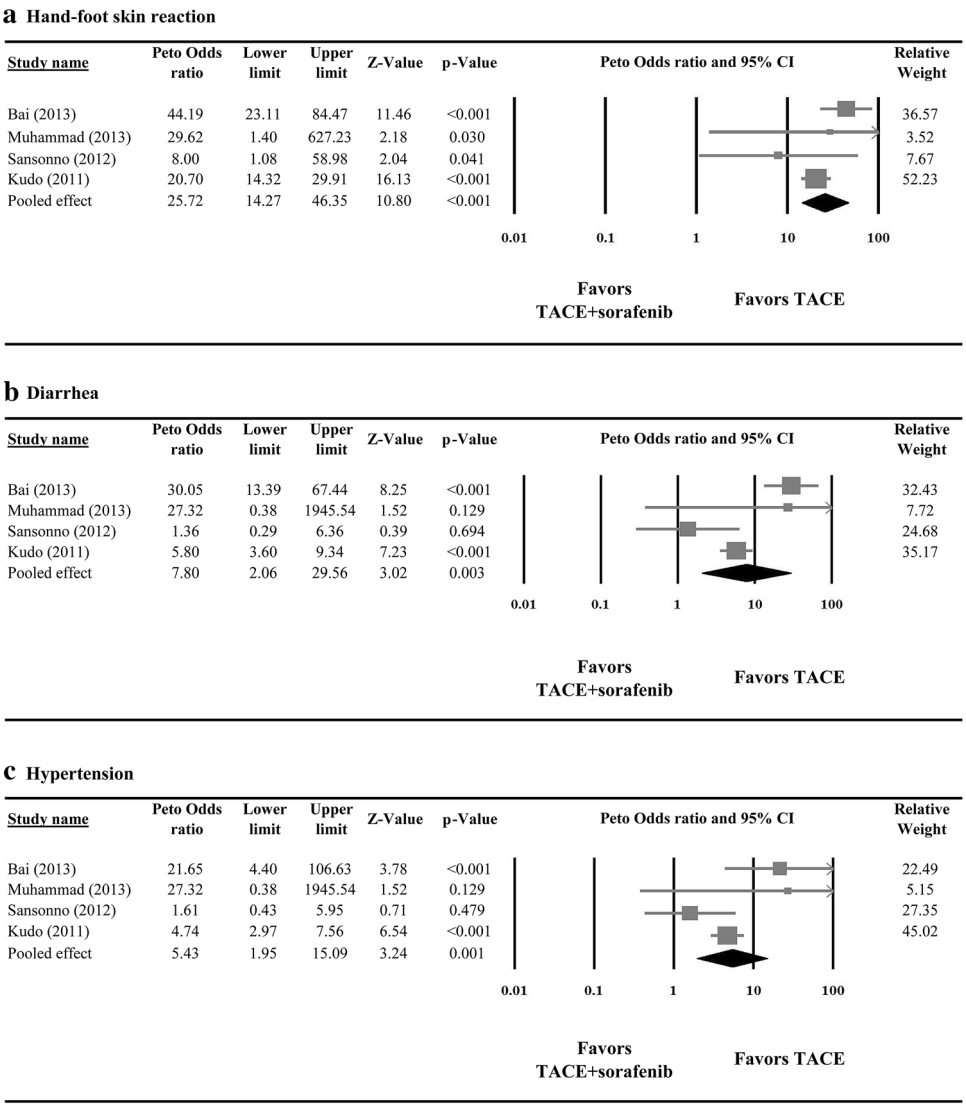

Fig. 4 Sensitivity analysis for treatment effects of sorafenib in combination with TACE on progression-free survival by the leave-one-out approach

improved TTP but not OS. The common adverse events associated with TACE + sorafenib treatment were fatigue, diarrhea, nausea, hand-foot skin reactions, alopecia, rash, and hypertension.

Several recent meta-analyses have also evaluated the use of TACE + sorafenib in treating patients with unresectable HCC [5, 33–35]. Yang et al. included 6 studies that together had 1181 patients [35]. Similar to our findings, they found that the pooled HR for the randomized control trials for OS did not reach statistical significance. However, when they also included retrospective studies, they found the HR did reach statistical significance for the TACE + sorafenib treatment (HR 0.64; 95 % CI 0.43–0.97). Yang et al. also evaluated time to progression (TTP) and response to treatments. They found that TACE + sorafenib resulted in longer TTP and better response to treatment than TACE alone. Also similar to our findings and those of Yang et al., the meta-analysis of Liu et al. [32] found that TACE + sorafenib did not benefit OS [33]. Their analysis included seven comparative studies. The HR for OS was 0.81 ($p = 0.061$). Similar to Yang et al., they did find that TACE + sorafenib benefited TTP (HR 0.76; $p < 0.001$).

In contrast to our findings and those of Yang et al. and Liu et al., the meta-analysis of Fu et al. [33] found a benefit in survival with the addition of sorafenib to TACE [34]. Fu et al. included 9 studies in their meta-analysis with 900 patients. They found TACE + sorafenib significantly reduced 6-month and 1-year mortality ($p \leq 0.007$) but did not decrease 2-year mortality ($p = 0.46$) compared with TACE alone. In contrast to our analysis, they did not find a benefit of adding sorafenib to TACE for the 6-month TTP ($p = 0.06$). However, they did find that the objective response ratio ($p = 0.008$) and clinical benefit ratio ($p < 0.0001$) favored the combination therapy. Similar to

Table 4 Sensitivity analysis for treatment effects of sorafenib in combination with TACE

Study name	Statistics with study removed				
	Points	Lower limit	Upper limit	*Z* value	*p* value
A. TTP					
Bai et al. [29]	0.60	0.28	1.29	−1.31	0.191
Sansonno et al. [28]	0.74	0.52	1.06	−1.62	0.105
Kudo et al. [27]	0.50	0.33	0.74	−3.46	0.001
B. OS					
Bai et al. [29]	1.00	0.68	1.45	−0.02	0.986
Muhammad et al. [30]	0.79	0.46	1.36	−0.83	0.405
Kudo et al. [27]	0.64	0.46	0.90	−2.58	0.010
C. Hand-foot skin reactions					
Bai et al. [29]	20.17	14.08	28.90	16.38	<0.001
Muhammad et al. [30]	25.33	12.71	50.48	9.19	<0.001
Sansonno et al. [28]	28.33	15.36	52.27	10.70	<0.001
Kudo et al. [27]	30.71	11.68	80.70	6.95	<0.001
D. Diarrhea					
Bai et al. [29]	4.09	1.28	13.06	2.38	0.017
Muhammad et al. [30]	6.97	1.67	29.21	2.66	0.008
Sansonno et al. [28]	13.67	3.18	58.80	3.51	<0.001
Kudo et al. [27]	9.07	0.77	107.23	1.75	0.080
E. Hypertension					
Bai et al. [29]	3.71	1.54	8.94	2.93	0.003
Muhammad et al. [30]	5.00	1.66	15.09	2.86	0.004
Sansonno et al. [28]	8.62	2.58	28.81	3.50	<0.001
Kudo et al. [27]	7.31	0.88	60.66	1.84	0.066

Fu et al., a meta-analysis by Zhang et al. [34] found TACE + sorafenib improved OS (HR = 0.65; $p = 0.007$) [35]. Zhang et al. included seven comparative studies. They also found TACE + sorafenib improved TTP (HR 0.68; $p = 0.003$) and ORR (HR 1.06; $p = 0.021$).

In the four prior meta-analyses the incidence of adverse events was higher in the TACE + sorafenib group than in the TACE alone group [33–35]. Similar to our findings, the other meta-analyses found that common adverse events associated with TACE + sorafenib were hand-foot skin reactions, diarrhea, hypertension, rash, and fatigue.

The difference across the meta-analyses likely reflects the different studies included and different methods of analyses. The findings of all the meta-analyses, including our own, are limited by the small number of included studies (range 4–9 comparative studies). Regardless, all the studies indicate that TACE + sorafenib may bring a benefit to patients with unresectable HCC compared to TACE alone. Our study was also limited by the high heterogeneity among the studies used in the meta-anlaysis and the fact that the pooled HR for TTP was not significant when either the study of Sansone et al. [28] or Bai et al. [29] was removed. Of the three studies included in the OS analysis, only Kudo et al. [27] found the TTP not to be significantly different between TACE + sorafenib and TACE alone [29]. However, in the study of Kudo et al., [27] sorafenib was given 1–3 months following embolization. Kudo et al. [27] speculate that the reason for the OS finding may reflect the delay in starting sorafenib after TACE and/or the lower daily dose of sorafenib (200 mg twice daily used in their study vs. 400 mg twice daily in the other trials) [6]. Consistent with this, subgroup analysis indicated that several factors might affect TTP including the age, treatment lag, treatment duration, number of prior TACE courses, and administration dose [27]. Another limitation of our analysis was not all the included studies in the meta-analysis were randomized controlled trials, and we did not take into consideration differences in clinical characteristics across the studies such as Child-Pugh stage, HBV or HCV infection, dose of sorafenib, treatment length of sorafenib, and concurrent chemoembolization (doxorubicin, mitomycin, etc.). Finally, there were differences across the studies in the definition of complete response. One study defined complete response (CR) using the mRECIST criteria [30]; another defined CR using the RECIST criteria [29]. Kudo et al. [27] defined CR as 100 % tumor necrosis or shrinkage, and Sansonno et al. [28] defined it as the absence of contrast enhancement within the original tumor.

According to BCLC, many of the patients in our study had intermediate HCC; the inclusion criteria for the studies selected for patients diagnosed unresectable HCC with Child-Pugh class A or B, ECOG 0–1, and limitations of tumor size. Patients with intermediate HCC represent a heterogeneous population with different liver functions and tumor burdens. It is possible that TACE was effective in a subgroup of this population and that some patients may have benefited from other treatments.

In summary, our meta-analysis found that TACE + sorafenib can improve TTP. We did not find the combined therapy improved OS. Additional randomized controlled studies are necessary to further investigate the clinical benefit of TACE + sorafenib in treating advanced HCC.

Compliance with ethical standards

Funding None.

Conflict of interest Guiliang Wang, Yan Liu, Shu-feng Zhou, Ping Qiu, Linfang Xu, Ping Wen, Jianbo Wen, and Xianzhong Xiao declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Waller LP, Deshpande V, Pyrsopoulos N. Hepatocellular carcinoma: a comprehensive review. World J Hepatol. 2015;7:2648–63.
2. Chang MH. Prevention of hepatitis B virus infection and liver cancer. Recent Results Cancer Res. 2014;193:75–95.
3. Lencioni R, Chen XP, Dagher L, Venook AP. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? Oncologist. 2010;15(Suppl 4): 42–52.
4. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132: 2557–2576.
5. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis. 2010;30:61–74.
6. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol. 2006;12:7561–7567.
7. Chuan-Xing L, Xu H, Bao-Shan H, Yong L, Pei-Jian S, Xian-Yi Y, et al. Efficacy of therapy for hepatocellular carcinoma with portal vein tumor thrombus: chemoembolization and stent combined with iodine-125 seed. Cancer Biol Ther. 2011;12:865–71.
8. Kasai K, Ushio A, Kasai Y, Sawara K, Miyamoto Y, Oikawa K, et al. Combination therapy of intra-arterial 5-fluorouracil and systemic pegylated interferon alpha-2b for advanced hepatocellular carcinoma. Int J Clin Oncol. 2011;16:221–229.
9. Katamura Y, Aikata H, Takaki S, Azakami T, Kawaoka T, Waki K, et al. Intra-arterial 5-fluorouracil/interferon combination therapy for advanced hepatocellular carcinoma with or without three-dimensional conformal radiotherapy for portal vein tumor thrombosis. J Gastroenterol. 2009;44:492–502.
10. Uka K, Aikata H, Takaki S, Miki D, Jeong SC, Hiramatsu A, et al. Similar effects of recombinant interferon-alpha-2b and natural interferon-alpha when combined with intra-arterial 5-fluorouracil for the treatment of advanced hepatocellular carcinoma. Liver Int. 2007;27:1209–1216.
11. Zhang XB, Wang JH, Yan ZP, Qian S, Du SS, Zeng ZC. Hepatocellular carcinoma with main portal vein tumor thrombus: treatment with 3-dimensional conformal radiotherapy after portal vein stenting and transarterial chemoembolization. Cancer. 2009;115:1245–1252.
12. Lin CS, Jen YM, Chiu SY, Hwang JM, Chao HL, Lin HY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. Jpn J Clin Oncol. 2006;36:212–217.
13. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Treatment outcomes for hepatocellular carcinoma using chemoembolization in combination with other therapies. Cancer Treat Rev. 2006;32:594–606.
14. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002; 359:1734–1739.
15. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37:429–442.
16. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. World J Gastroenterol. 2004;10:2878–2882.
17. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000;407:249–257.
18. Sergio A, Cristofori C, Cardin R, Pivetta G, Ragazzi R, Baldan A, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol. 2008;103:914–921.
19. Nexavar (sorafenib). 2010; available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021923s008s009lbl.pdf.
20. Strebel BM, Dufour JF. Combined approach to hepatocellular carcinoma: a new treatment concept for nonresectable disease. Expert Rev Anticancer Ther. 2008;8:1743–1749.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65–W94.
22. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;15;23(9):1351–1375.
23. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med. 1998 30;17(8):841–856.
24. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol. 1999;150:206–215.
25. National Research Council. Combing Information: Statistical Issues and Opportunities for Research. Washington, DC: National Academy Press; 1992.
26. Qu XD, Chen CS, Wang JH, Yan ZP, Chen JM, Gong GQ, et al. The efficacy of TACE combined sorafenib in advanced stages hepatocellullar carcinoma. BMC Cancer. 2012;12:263.
27. Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer. 2011;47: 2117–2127.
28. Sansonno D, Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a

sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. Oncologist. 2012;17:359–663.
29. Bai W, Wang YJ, Zhao Y, Qi XS, Yin ZX, He CY, et al. Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: a propensity score matching study. J Dig Dis. 2013;14:181–190.
30. Muhammad A, Dhamija M, Vidyarthi G, Amodeo D, Boyd W, et al. Comparative effectiveness of traditional chemoembolization with or without sorafenib for hepatocellular carcinoma. World J Hepatol. 2013;5:364–371.
31. Common terminology criteria for adverse events. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
32. Liu L, Chen H, Wang M, Zhao Y, Cai G, Qi X, et al. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. PLoS One. 2014;9:e91124.
33. Fu QH, Zhang Q, Bai XL, Hu QD, Su W, Chen YW, et al. Sorafenib enhances effects of transarterial chemoembolization for hepatocellular carcinoma: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014;140:1429–1440.
34. Zhang L, Hu P, Chen X, Bie P. Transarterial chemoembolization (TACE) plus sorafenib versus TACE for intermediate or advanced stage hepatocellular carcinoma: a meta-analysis. PLoS One. 2014;9:e100305.
35. Yang M, Yuan JQ, Bai M, Han GH. Transarterial chemoembolization combined with sorafenib for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Mol Biol Rep. 2014;41:6575–6582.