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ORIGINAL ARTICLE

Efficacy and safety of sorafenib combined with TACE in the treatment of advanced hepatocellular carcinoma: A meta-analysis

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Summary

Purpose: *Sorafenib combined with transcatheter arterial chemoembolization (TACE) is one of the common methods in the clinical treatment of advanced hepatocellular carcinoma (HCC), but its efficacy and safety are still controversial. Therefore, we used meta-analysis to evaluate the efficacy and safety of sorafenib combined with TACE in the treatment of advanced HCC.*

Methods: *Up to March 14, 2021, the databases of PubMed, EMBASE, Cochrane Library, CNKI and Wanfang were searched, and the randomized controlled clinical trials (RCTs) of sorafenib combined with TACE in the treatment of primary HCC were included. Two researchers independently screened the literature, extracted data and evaluated the quality according to the inclusion and exclusion criteria. Revman5.4 software was used for meta-analysis.*

Results: *A total of 3076 patients were included in 23 studies, including sorafenib combined with TACE group (n=1542) and TACE group (n=1534). The results of meta-analysis showed that sorafenib combined with TACE could increase the objective response rate (ORR) (RR=1.35, 95%CI: 1.24-1.48, p<0.00001), disease control rate (DCR) (RR=1.19, 95%CI: 1.11-1.28, p<0.00001), prolong the time of disease progression (TTP) (HR=0.80, 95%CI: 0.70-0.92, p=0.001), reduce the expression level of alpha-fetoprotein (AFP) (SMD=2.01, 95%CI: 1.27-2.75, p<0.00001) and vascular endothelial growth factor (VEGF) (SMD=2.62, 95% CI: 1.35-3.90, p<0.0001) in serum. However, the overall survival (OS) was not prolonged (HR=0.86, 95%CI: 0.73-1.02, p=0.09). The incidences of fatigue, diarrhea, elevated bilirubin, skin reaction of hands and feet, rash, hypertension and oral mucosal inflammation in sorafenib combined with TACE group were higher than those in TACE group (p<0.05).*

Conclusion: *Sorafenib combined with TACE has some clinical benefits compared with TACE alone, but it does not seem to prolong the OS of patients with HCC, and the incidence of adverse reactions is higher, so more high-quality RCTs are needed to further study the efficacy of the combination regimen.*

Key words: *hepatocellular carcinoma, liver cancer, sorafenib, transcatheter arterial chemoembolization, meta-analysis, sorafenib, TACE.*

Introduction

According to the annual statistics of GLOBOCAN 2018, primary hepatocellular carcinoma (HCC) has the sixth-highest incidence of cancer and the fourth-highest mortality in the world [1]. Surgical treatment of early liver cancer is the main treatment, and the cure rate can reach 80.5% [2]. However, there are often no clinical symptoms in the early stage of liver cancer, and the condition

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has often progressed to the middle and late stages, and the best time for surgical treatment has been lost. Transcatheter arterial chemoembolization (TACE) is the main method for the treatment of unresectable advanced liver cancer, which mainly causes tumor cell ischemia and hypoxic necrosis by occluding the blood vessels of the tumor tissue. However, clinical studies have proved that the tumor remains easily to recur and the long-term effect is poor after TACE [3]. Tumor recurrence is closely related to neovascularization, and sorafenib, as an oral polykinase inhibitor, can effectively inhibit tumor angiogenesis and tumor cell proliferation, thus reducing tumor cell recurrence and metastasis [4]. Therefore, the combination of sorafenib and TACE may improve the clinical outcome of patients with advanced liver cancer. In recent years, many studies have reported sorafenib combined with TACE in the treatment of HCC, but its efficacy and safety are controversial. Therefore, in this study, meta-analysis was used to analyze the efficacy and safety of sorafenib combined with TACE in the treatment of advanced primary HCC, to provide a reference for clinical application

Methods

Publication search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The systematic literature search was performed through PubMed, EMBASE, Cochrane Library,CNKI and WanFang database, covering all articles published up to March 14, 2021. The following keywords were used to retrieve articles: Liver neoplasms, liver cancer, hepatocellular carcinoma, HCC and sorafenib and transcatheter arterial chemoembolization, TACE. References of the retrieved publications were also screened. The language was English or Chinese. Only published studies with full-text articles were included.

Literature inclusion and exclusion criteria

Inclusion criteria: (1) the included study design was randomized controlled, regardless of blind method, the patients were divided into Sorafenib plus TACE group and TACE group alone; (2) the subjects were pathologically or clinically diagnosed that HCC could not be subjected by surgical resection; (3) the short-term and long-term efficacy and adverse reactions of the two groups of cases were available; (4) the literature was published in Chinese or English; (5) the literature was an original study and could provide original data.

Exclusion criteria: (1) reviews, case reports, conference summaries, non-clinical reports and repeated studies; (2) the data were incomplete and the original data were not available; (3) the number of cases were <50; (4) non-RCT studies; (5) low-quality literature with Jadad scores less than 3.

Assessment of included studies

The quality of the included RCTs was evaluated by Jadad scale [5] from three aspects: randomization, blind, withdrawal and loss of follow-up, with a full score of 5, 0-2 as low-quality research and 3-5 as high-quality research. The quality evaluation was conducted independently by two investigators (Dailong Li and Yaqi Pang) at the same time, and cross-checked. In case of disagreement, it was decided by discussion or referring to the opinion of the third researcher (Xinhua Xu).

Data extraction

The articles were independently reviewed by two investigators (Dailong Li and Yaqi Pang) to extract data and cross-checked. In case of differences, their fate was decided by discussion or reference to the third researcher (Xinhua Xu). The extracted data mainly included: (1) general data, such as title, first author, publication date and literature source; (2) characteristics of study subjects, chemoembolization agent and dose, oral dose of sorafenib and treatment time; (3) observation indicators, such as short-term efficacy, long-term efficacy, serum tumor marker levels and adverse reactions; (4) if the hazard ratio (HR) and 95% confidence interval (CI) were not directly provided in the original text, according to the method provided by Tierney et al[6], Getdata Dragh Digitizer Software was used to extract the data from the Kaplan-Meier survival curve, and the HR and 95% CI values were analyzed and calculated. If the report was unknown or had lack of information, we tried to contact the author by email to obtain further unpublished data.

Statistics

The Review Manager version 5.4 software for data processing was used. The relative risk (RR) and 95%CI were used as evaluation indexes for the two classifica-

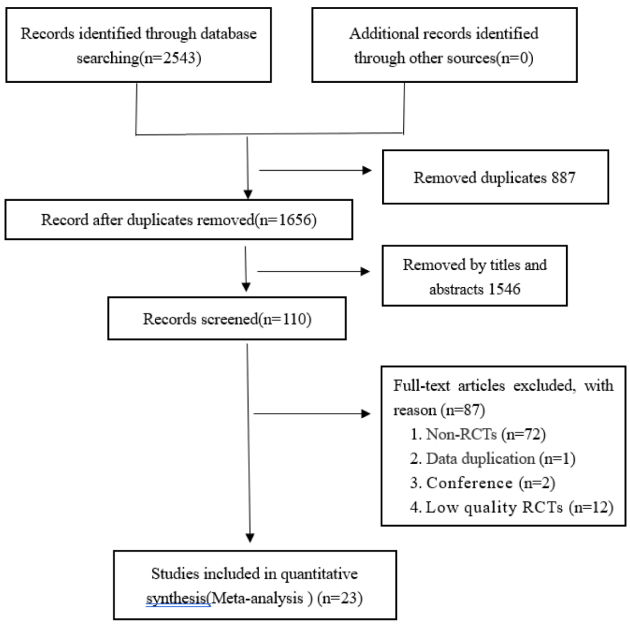

Figure 1. Literature screening flow chart.

tion data. The HR and 95%CI were used for the evaluation of survival data. For continuous variables, standard mean difference (SMD) and 95%CI were used for effect pooled analysis, and the forest map was drawn for meta-analysis. All p values were 2-sided, and $p<0.05$ was considered significant. Fixed-effects model was adopted when there was no evidence of significant heterogeneity ($p>0.1$ and $I^2<50\%$); otherwise, random-effects model was used. Sensitivity analysis was used to test the stability of the results and funnel plots were used to evaluate publication bias. If possible, heterogeneity was explored and subgroup analyses were performed.

Results

Literature search and study characteristics

A total of 2543 articles were retrieved, and 887 repeated articles were excluded by title, year and author information. Then after reading abstracts and full-text screening, 1633 articles that did not meet the criteria were excluded and finally 23 studies were included [7-29] (Figure 1). Of the 3076 patients with primary liver cancer, 1542 received sorafenib combined with TACE and 1534 received TACE alone. The quality evaluation of the included studies are shown in Table 1, all of which are of high quality. The key baseline characteristics of patients are fully described in all the included studies, as shown in Table 2.

Objective response rate (ORR)

Twenty-one studies [7-23,25-28] provided ORR of patients with HCC, and heterogeneity test showed low heterogeneity among studies ($p=0.17$, $I^2=23\%$). The fixed effect model analysis showed that the ORR of sorafenib combined with TACE group was higher than that of TACE group (RR=1.35, 95%CI: 1.24-1.48, $p<0.00001$) (Figure 2).

Disease control rate (DCR)

DCR was provided in 21 included studies [7-23,25-28], and heterogeneity test showed significant heterogeneity among the studies ($p=0.0003$, $I^2=60\%$). The random-effects model analysis showed that the DCR of sorafenib combined with TACE group was higher than that of TACE group, and the difference was statistically significant (RR=1.19, 95%CI: 1.11-1.28, $p<0.00001$) (Figure 3).

Table 1. Jadad scoring scale included in the study

Author	*Published date*	*Randomization*	*blind*	*Withdrawal and loss of follow-up*	*Total score*
H Sun	2014	2	1	1	4
D Lv	2019	2	1	1	4
QY Hu	2019	1	1	1	3
K Yang	2015	2	1	1	4
XT Xu	2016	2	1	1	4
DP Bi	2016	1	1	1	3
JD Wu	2015	2	1	1	4
J Yan	2019	2	1	1	4
HY Jiang	2010	2	1	1	4
SM Chen	2012	1	1	1	3
LJ Yan	2017	2	1	1	4
RG Zhou	2014	1	1	1	3
TY Wei	2016	2	1	1	4
JH Xie	2015	2	1	1	4
BE Shao	2019	1	1	1	3
CS Huang	2017	2	1	1	4
BC Gao	2018	2	1	1	4
Kudo	2011	1	1	1	3
Kudo	2019	2	1	1	4
Lencioni	2016	2	2	1	5
Meyer	2017	2	2	1	5
Hoffmann	2015	2	2	1	5
Sansonno	2012	2	1	1	4

Table 2. Basic characteristics of the included literature

Study	*Country*	*Group*	*Number of cases*	*Gender (male/female)*	*Age*	*Child-Pugh (A/B/C)*	*ECOG /KPS score*	*BCLC (A/B/C)*	*HBV/HCV*	*Days of taking sorafenib*	*Daily dose of sorafenib*
H Sun 2014	China	Sorafenib+TACE VS. TACE	81 81	68/13 66/15	25-76 24-76	70/11/0 72/9/0	NA	NA	NA	NA	800mg
D Lv 2019	China	Sorafenib+TACE VS. TACE	60 60	38/22 40/20	50.8 51.4	42/18/0 44/16/0	NA	0/36/14 0/34/16	NA	56d-210d	800mg
QY Hu 2019	China	Sorafenib+TACE VS. TACE	39 39	27/12 25/14	53.5 53.2	29/10/0 30/9/0	KPS≥60 KPS≥60	NA	NA	NA	800mg
K Yang 2015	China	Sorafenib+TACE VS. TACE	74 74	56/18 60/14	59.3 58.4	69/5/0 68/6/0	KPS:77.95 KPS:78.04	NA	NA	NA	800mg
XT Xu, 2016	China	Sorafenib+TACE VS. TACE	40 39	31/9 27/12	35-76 38-76	34/6/0 30/9/0	ECOG:0-2 ECOG:0-2	-/-/15 -/-/12	NA	180d	800mg
DP Bi, 2016	China	Sorafenib+TACE VS. TACE	57 57	33/24 35/22	48-72 49-76	NA	KPS:54.6 KPS:55.0	NA	NA	NA	800mg
JD Wu 2015	China	Sorafenib+TACE VS. TACE	58 57	38/20 32/25	NA	36/22/0 30/27/0	ECOG:0-2 ECOG:0-2	NA	HBV(54) HBV(52)	NA	800mg
J Yan, 2019	China	Sorafenib+TACE VS. TACE	46 46	30/16 28/18	42-68 45-66	NA	NA	NA	NA	180d	NA
HY Jiang 2019	China	Sorafenib+TACE VS. TACE	30 30	24/6 23/7	56 58	25/5/0 24/6/0	KPS≥60 KPS≥60	NA	NA	≥180d	800mg
SM Chen 2012	China	Sorafenib+TACE VS. TACE	28 28	20/8 17/11	NA	15/13/0 16/12/0	ECOG:0-2 ECOG:0-2	0/16/12 0/18/10	NA	NA	800mg
LJ Yan 2017	China	Sorafenib+TACE VS. TACE	48 48	37/11 35/13	42.95 43.06	29/19/0 31/17/0	ECOG:0-2 ECOG:0-2	NA	NA	NA	800mg
RG Zhou 2014	China	Sorafenib+TACE VS. TACE	48 48	34/14 31/17	49-85 43-78	NA	NA	0/0/48 0/0/48	NA	NA	800mg
TY Wei 2016	China	Sorafenib+TACE VS. TACE	40 41	29/11 30/11	45-70 46-70	30/10/0 30/11/0	ECOG:0-2 ECOG:0-2	NA	NA	NA	800mg
JH Xie 2015	China	Sorafenib+TACE VS. TACE	43 40	34/9 30/10	NA	30/13/0 28/12/0	NA	NA	NA	NA	800mg
BE Shao 2019	China	Sorafenib+TACE VS. TACE	82 82	55/27 54/28	57.74 57.37	69/13/0 72/10/0	ECOG:0-2 ECOG:0-2	0/27/55 0/25/57	NA	84d	800mg
CS Huang 2017	China	Sorafenib+TACE VS. TACE	60 60	43/17 44/16	52-84 53-85	NA	NA	NA	NA	84d	800mg
BC Gao 2018	China	Sorafenib+TACE VS. TACE	33 33	27/6 28/5	52-76 51-76	23/10/0 24/9/0	ECOG:0-2 ECOG:0-2	0/0/33 0/0/33	NA	NA	800mg
Kudo 2011	Janpan, Korea	Sorafenib+TACE VS. TACE+Placebo	229 229	174/55 168/61	69 70	229/0/0 229/0/0	ECOG:0-1 ECOG:0-1	NA	HBV(47) HCV(144) HBV(52) HCV(139)	120d 141d	400mg
Kudo 2019	Janpan	Sorafenib+TACE VS. TACE	80 76	63/17 55/21	72 73	79/1/0 71/5/0	ECOG:0-1 ECOG:0-1	27/44/9 33/34/9	HBV(10) HCV(38) HBV(2) HCV(53)	271d	400mg
Lencioni 2016	Global multicenter	Sorafenib+TACE VS. TACE+Placebo	154 153	135/19 126/27	64.5 63	153/1/0 152/0/1	ECOG:0 ECOG:0	NA	HBV(55) HCV(39) HBV(50) HCV(41)	200d	800mg
Meyer 2017	UK	Sorafenib+TACE VS. TACE+Placebo	157 156	139/18 138/18	65 68	145/5/7 148/3/5	ECOG:0-1 ECOG:0-1	NA	HBV(7) HCV(15) HBV(7) HCV(9)	120d	800mg
Hoffmann 2015	Germany	Sorafenib+TACE VS. TACE+Placebo	24 26	45/5	58.5 58	14/9/1 20/6/0	NA	NA	HBV(3) HCV(11) HBV(3) HCV(7)	125d	800mg
Sansonno 2012	Italian	Sorafenib+TACE VS. TACE+Placebo	31 31	18/13 19/12	73 72.8	31/0/0 31/0/0	ECOG:0-1 ECOG:0-1	0/31/0 0/31/0	HCV(31) HCV(31)	NA	NA

The time of disease progression (TTP)

Six studies [24-29] reported that the results of TTP, heterogeneity test showed low heterogeneity (p=0.17, I^2=35%). The fixed effect model analysis showed that the TTP (HR=0.80,95%CI:0.70-0.92,p=0.001) of patients with HCC was prolonged in sorafenib combined with TACE group than in TACE group (Figure 4).

Overall survival (OS)

Seven studies were included [8, 10, 13, 20, 24, 26, 27]. The results of OS in the heterogeneity test

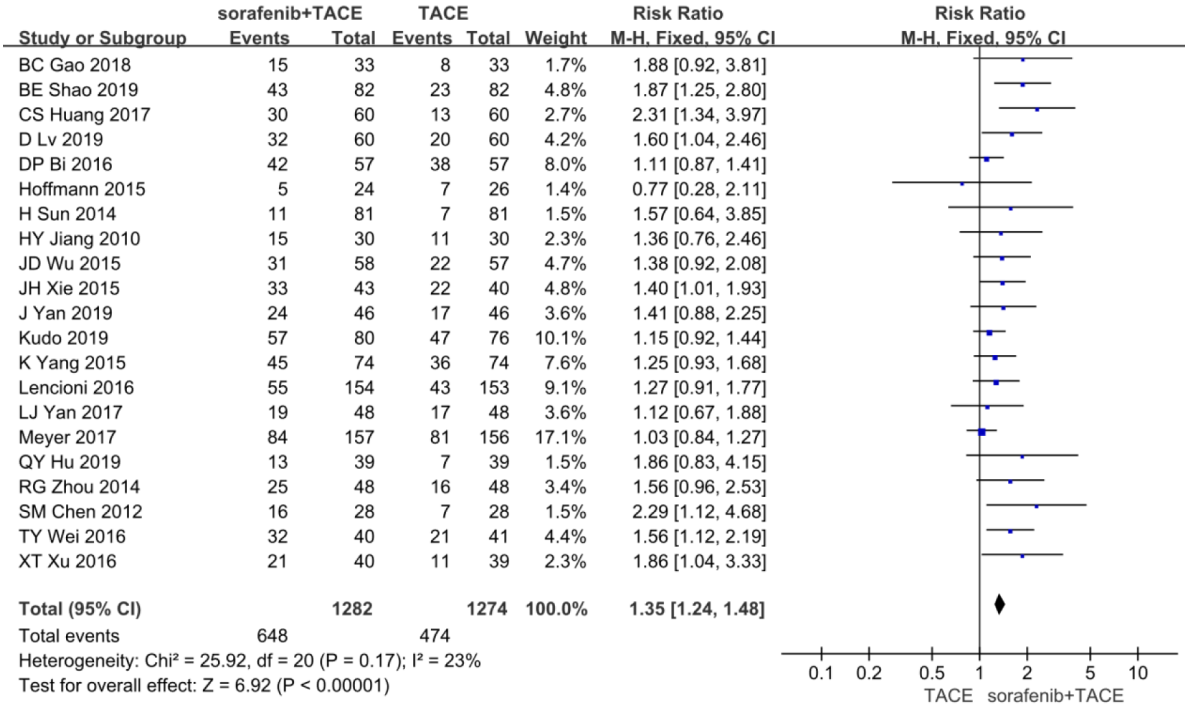

Figure 2. ORR of sorafenib combined with TACE versus TACE alone in HCC.

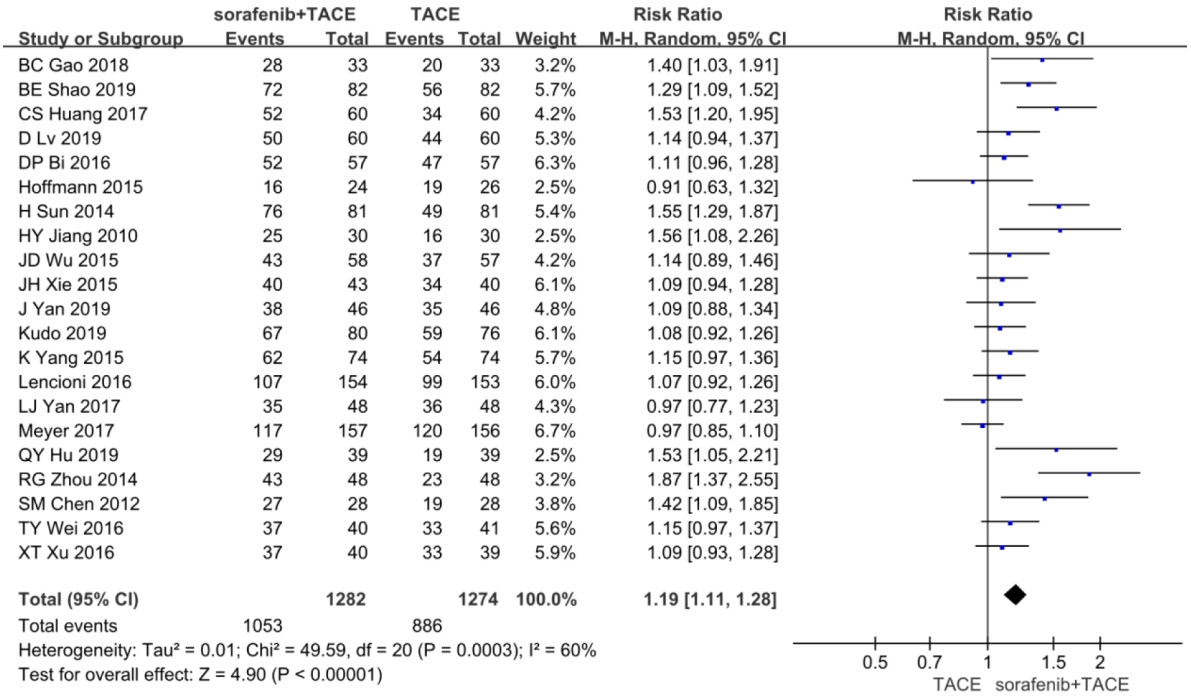

Figure 3. DCR of sorafenib combined with TACE versus TACE alone in HCC.

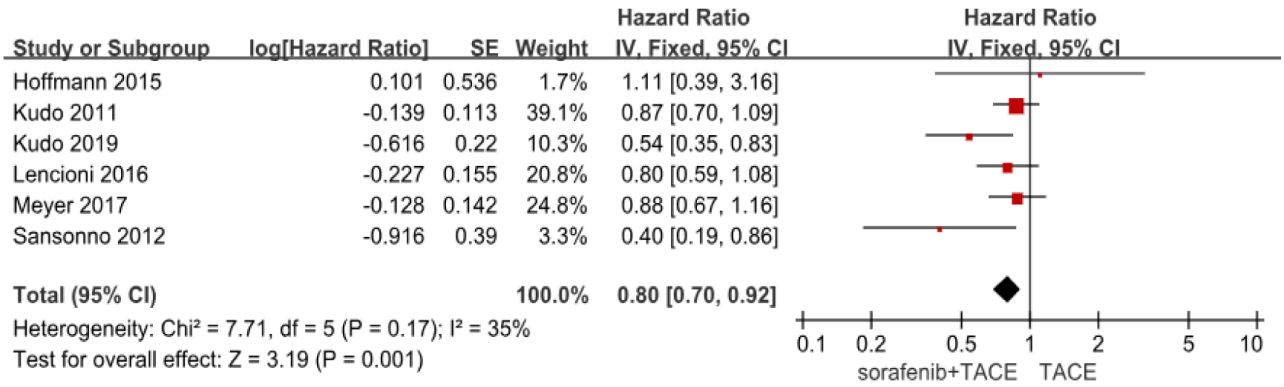

Figure 4. TTP of sorafenib combined with TACE versus TACE alone in HCC.

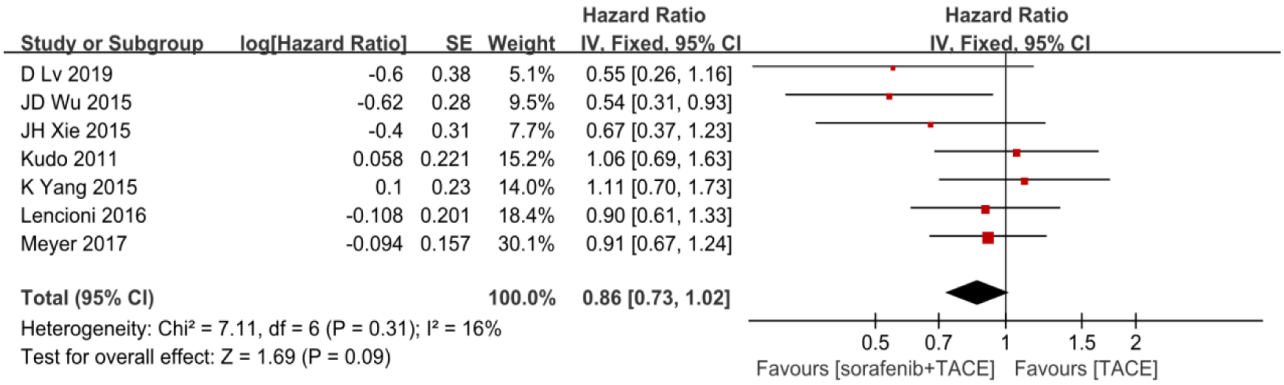

Figure 5. OS of sorafenib combined with TACE versus TACE alone in HCC.

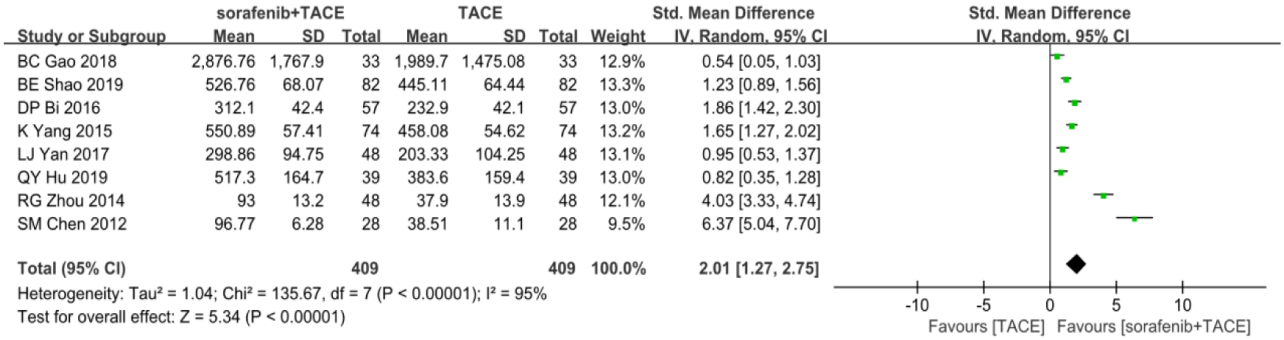

Figure 6. AFP of sorafenib combined with TACE versus TACE alone in HCC.

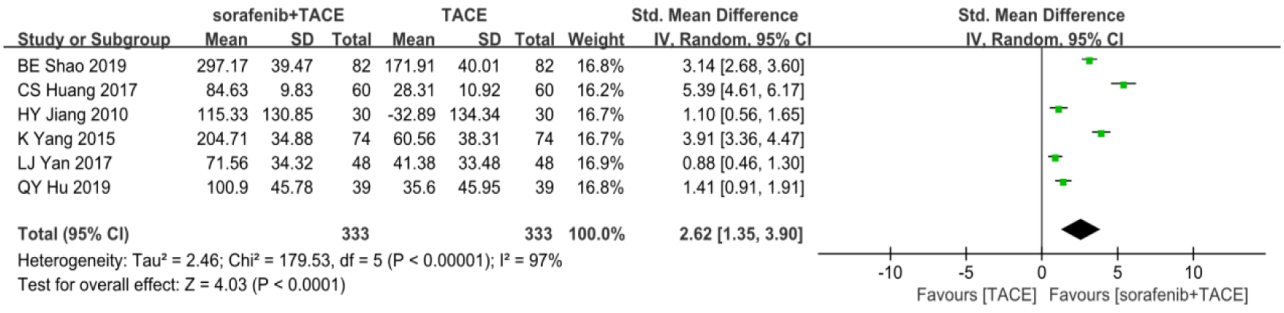

Figure 7. VEGF of sorafenib combined with TACE versus TACE alone in HCC.

showed that the heterogeneity among the studies was low (p=0.31, I^2=16%). The fixed effect model analysis showed that there was no significant difference in OS, between sorafenib combined with TACE group and the TACE alone group in the treatment of HCC (HR=0.86, 95%CI: 0.73-1.02, p=0.09) (Figure 5).

AFP and VEGF

Eight and six studies reported the expression levels of AFP and VEGF in serum before and after treatment, respectively based on the results of heterogeneity test (AFP p<0.00001, I^2=95%; VEGF p<0.00001, I^2=97%). The random effect model analysis showed that sorafenib combined with TACE group significantly decreased the expression levels of AFP and VEGF in serum of HCC patients compared with the TACE alone group, and the difference was statistically significant (AFP SMD=2.01, 95%CI: 1.27~2.75, p<0.00001; VEGF SMD=2.62, 95%CI: 1.35-3.90, p<0.0001) (Figures 6, 7).

Adverse events

The incidences of fatigue, diarrhea, bilirubin elevation, hand and foot skin reaction, rash, hypertension and oral mucosal inflammation in sorafenib plus TACE group were significantly higher than those in TACE group (p<0.05). There was no significant difference in the incidence of fever, anorexia, abdominal pain, nausea, vomiting, elevated ALT or AST, alopecia, leukopenia and thrombocytopenia between sorafenib plus TACE group and TACE alone group (Table 3).

Table 3. Comparison of adverse reactions of sorafenib combined with TACE and TACE alone in the treatment of primary HCC

Adverse reaction	*Number of studies*	*Heterogeneity*	*RR 95%CI*	*p*
Fatigue	10	p=0.12, I2=36%	1.17(1.05-1.31)	0.005
Fever	10	p=0.75, I2=0%	1.00(0.91-1.11)	0.93
Anorexia	6	p=0.68, I2=0%	1.17(0.96-1.43)	0.11
Diarrhoea	14	p<0.00001, I2=77%	2.49(1.65-3.74)	<0.0001
Abdominal pain	7	p=0.84, I2=0%	1.03(0.91-1.16)	0.64
Nausea	5	p=0.24, I2=28%	1.00(0.82-1.22)	0.99
Vomit	4	p=0.15, I2=44%	0.92(0.69-1.21)	0.54
ALT elevation	3	p<0.00001, I2=92%	1.67(0.71-3.89)	0.24
Elevated bilirubin	3	p=0.48, I2=0%	1.43(1.11-1.83)	0.006
AST elevation	3	p<0.00001, I2=98%	1.86(0.47-7.37)	0.38
Alopecia	11	p<0.00001, I2=86%	2.01(0.98-4.13)	0.06
Hand and foot skin reaction	17	p<0.00001, I2=97%	6.87(2.66-17.71)	<0.0001
Rash	9	p=0.007, I2=62%	2.56(1.67-3.93)	<0.0001
hypertension	12	p=0.001, I2=64%	1.99(1.31-3.03)	0.001
Leukopenia	4	p=0.96, I2=0%	1.12(0.89-1.40)	0.34
Oral mucosal inflammation	5	p=0.29, I2=20%	3.46(2.34-5.11)	<0.00001
Thrombocytopenia	3	p<0.00001, I2=96%	2.34(0.56-9.82)	0.25

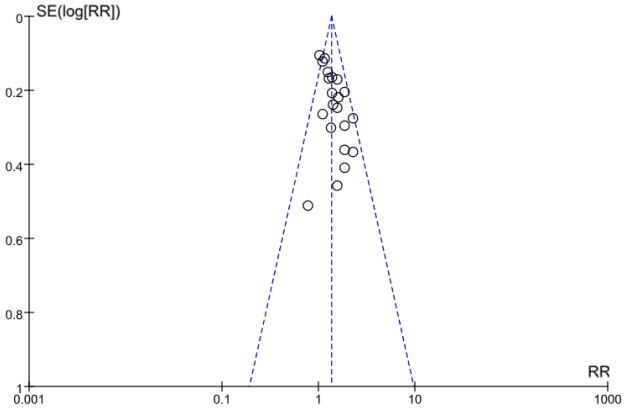

Figure 8. Funnel plot of ORR.

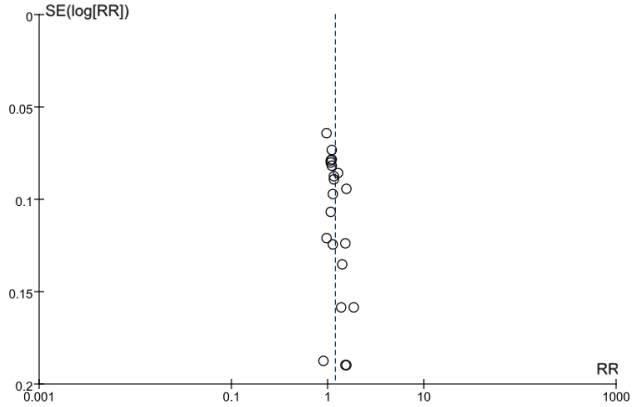

Figure 9. Funnel plot of DCR.

Sensitivity analysis and publication bias

Sensitivity analysis was performed for each meta-analysis, and one study was deleted at a time to assess the stability of the results. These analyses showed that the corresponding HR and RR values did not change obviously, indicating that our results were stable. Finally, the funnel plot was used to judge the bias degree of literature publication, and the funnel plot did not show any obvious evidence of asymmetry, suggesting that the possibility of publication bias is low (Figures 8,9).

Discussion

As a representative drug of molecular targeted therapy for advanced HCC, sorafenib has been proved to improve the OS of advanced HCC patients in different regions compared with placebo in the past two large RCTs, thus establishing the first-line treatment status of sorafenib in advanced HCC. In both studies, however, sorafenib only prolonged OS for 3 months in patients with advanced HCC [30,31]. In the follow-up studies, the ORR of sorafenib is less than 5% [30,31], the improvement of patients' symptoms is not obvious, and the clinical effect is still limited. As one of the most effective treatment methods for advanced liver cancer [32], TACE can effectively destroy the main tumor and sub-focuses of the liver by reducing and blocking the blood supply of the tumor, and the short-term effect is significant. However, TACE can cause acute hypoxia and up-regulation of VEGF, which may contribute to revascularization, thus promoting tumor metastasis, recurrence and spread, and affecting the long-term effect. Sorafenib downregulates RAS/RAF/MEK/ERK signal transduction pathway and inhibits tumor cell proliferation and anti-angiogenesis by inhibiting vascular endothelial growth factor receptors (VEGFR-1,2,3) and platelet-derived growth factor receptors (PDGFR) [33,34]. Therefore, the principle of sorafenib combined with TACE in inhibiting revascularization and tumor proliferation is clear. The application of TACE combined with sorafenib has been explored in a series of clinical trials, in which sequential and simultaneous administration has been proved to be feasible and safe [24,26,27,35-37].

In recent years, there are many literature reports about the comparison of sorafenib combined with TACE and TACE alone in the treatment of primary HCC, but the efficacy and safety of sorafenib combined with TACE are still controversial. Therefore, this study collected the clinical RCTs literature of sorafenib combined with TACE versus TACE alone in the treatment of unresectable primary HCC, in order to summarize the efficacy and safety of sorafenib combined with TACE in the treatment of primary HCC. After screening the literatures according to the inclusion and exclusion criteria, a total of 23 RCTs studies (a total of 3076 patients) were included, all of which were treated with sorafenib combined with TACE compared with TACE alone. There was no obvious asymmetry in the funnel plot, suggesting that the publication bias was low. Our meta-analysis showed that sorafenib combined with TACE could increase ORR, DCR, prolong TTP, and reduce the expression of AFP and VEGF in serum, but compared with TACE alone, the combined regimen did not improve OS, and the risk of fatigue, diarrhea, elevated bilirubin, hand and foot skin reaction, rash, hypertension and oral mucosal inflammation was significantly increased in the combined regimen group. The occurrence of these adverse reactions in clinical treatment may lead to reduction and suspension of the dose of sorafenib, which may affect the benefits of sorafenib in adjuvant therapy.

Compared with the studies by Zhang et al [38], Li et al [39] and Hu et al [40], our meta-analysis included more and newer literature. Importantly, we excluded non-RCTs and included higher quality RCTs with higher level of evidence, thus making our articles more valuable for clinical reference. Of course, our study also has its own limitations: (1) although all the literature results included in this meta-analysis are RCT, with strict quality evaluation and screening, there are only few studies to analyze the western populations (only 4 studies, one of which is the global multicenter study); (2) the daily intake and duration of treatment of sorafenib and the mode of TACE are not completely consistent with the drugs of chemoembolization, resulting in potential heterogeneity; (3) the differences in the baseline characteristics of the patients included in the study, such as BCLC stage, ECOG score, etiology, etc., may also be the source of potential heterogeneity.

In conclusion, TACE combined with sorafenib is superior to TACE alone in improving ORR, DCR and prolonging TTP, but it has no obvious advantage in OS. Due to the inconsistent or missing original data provided by the present study, it is impossible to further analyze the factors that may affect the efficacy of treatment, such as BCLC stage of liver cancer, the duration of treatment with sorafenib and the sequence of treatment with TACE combined with sorafenib. In addition,

attention should be paid to the adverse reactions caused by the combination of drugs, as it may affect the progress of treatment and thus the efficacy of treatment. Based on this, the efficacy of TACE combined with sorafenib in the treatment of HCC needs to be further studied by more high-quality RCTs.

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Conflict of interests

The authors declare no conflict of interests.

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