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Sorafenib in combination with transarterial chemoembolization for hepatocellular carcinoma: a meta-analysis

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Abstract. – OBJECTIVE: This meta-analysis aimed to analyze the efficacy of sorafenib in combination with transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: Electronic data bases were searched for studies (1) enrolled HCC patients undergoing TACE; (2) with sorafenib therapy and control arm of no sorafenib therapy were included for meta-analysis and meta-regression; (3) studies without control arm were included for data review and (4) had time to progression (TTP) and overall survival (OS) or relative outcome of HCC as the endpoint. Meta-analysis and meta-regression were performed according to Cochrane guidelines.

RESULTS: Five studies (3 randomized trials, 1 cohort study and 1 prospective non- randomized controlled trial, totally 899 patients) were eligible for meta-analysis. The hazard ratio (HR) for TTP was 0.75 (95% CI: 0.48-1.03, $p = 0.003$) with significant heterogeneity (I2 = 82.7%) and for OS was 0.76 (95% CI: 0.47-1.05, $p = 0.147$) with slight heterogeneity (I2 = 47.9%). However, no covariate was found as independent predictor for better treatment efficacy. Hand-foot skin reaction, alopecia, rash/desquamation, diarrhea, hypertension, fatigue, anorexia, nausea and vomiting were common adverse events.

CONCLUSIONS: TACE combined with sorafenib has potential efficacy for HCC.

Key Words:
Sorafenib, Transarterial chemoembolization, Hepatocellular carcinoma, Meta-analysis.

Introduction

Hepatocellular carcinoma (HCC) is one of the lethal human cancers worldwide and its incidence matches mortality, reflecting the poor prognosis of this disease[1]. Major advances have been achieved in the surveillance, early diagnosis, and loco-regional therapy such as surgical resection and ablation therapy, which facilitate HCC treatment and improve the outcomes[2-4]. However, the recurrence rate of HCC is still high. Therefore, therapy to reduce HCC recurrence is definitely needed.

HCC is a stepwise process that involves the genetic alterations causing the activation of oncogenes and the inactivation of tumor suppressor genes. Sorafenib is an inhibitor of Raf/MEK/ ERK pathway, which appear to be particularly important in the development of HCC[5,6]. In addition, sorafenib inhibits tyrosine kinases including vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor-beta (PDGFR-beta) and Kit[7-9]. Thus, sorafenib is able to inhibit tumor growth and neoangiogenesis. Sorafenib has been approved by the FDA for advanced HCC systemic therapy. Recent randomized controlled trial showed that survival rate of patients with advanced HCC were 37% higher with sorafenib treatment compared to placebo treatment[10,11]. The clinical application focuses on the survival advantages of sorafenib alone and sorafenib combined treatment.

Transarterial chemoembolization (TACE) has become the standard care for patients with intermediate-stage disease (Barcelona Clinic Liver Cancer-B, BCLC-B)[8]. However, TACE elicits the secretion of VEGF and thus may promote tumor growth[12]. Therefore, whether combining TACE with systemic sorafenib therapy is an attractive approach for better HCC therapy remains a reasonable hypothesis.

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Here, we performed a literature review of available studies of TACE combined with sorafenib for HCC patients. Furthermore, we performed meta-analysis to identify the efficacy of the combined therapy approach and meta-regression analysis to identify relevant factors that can predict HCC outcome.

Materials and Methods

Study Selection

A systematic search of the published studies for sorafenib therapy for HCC patients was performed. The electronic databases included PubMed, Elsevier, Medline. The search strategy was a combination of the MESH terms "sorafenib", "TACE", and "carcinoma, hepatocellular". To identify more relevant studies, manual search was done in the reference lists of all identified papers (research articles and review papers).

Inclusion Criteria

The studies were selected for review if they fulfilled the following inclusion criteria: (1) trials that enrolled HCC patients who had undergone TACE; (2) consisting of sorafenib therapy and studies with a control arm of no sorafenib therapy were included for meta-analysis and meta-regression; (3) studies without control arm could be included for data review and (4) including time to progression (TTP) and overall survival (OS) or relative outcome of HCC as the endpoint. Two authors (M.D.H. and L.H.J.) performed search, evaluation, and summary independently. Discrepancies between authors were resolved through discussion.

Date Collection

The data of the following factors, if available, were extracted from each included study: patient age, male percentage, etiologies of underlying liver diseases, median tumor size, multiple tumors percentage (%), Child-Pugh classification, cirrhosis rate (%), Barcelona Clinic Liver Cancer (BCLC) stage, Eastern Cooperative Oncology Group performance status (ECOG PS), treatment characteristics, OS, TTP, progression-free survival (PFS) and adverse events.

Statistical Analysis

Meta-analysis was conducted with the consideration of random effects models. The natural logarithm of Hazard ratio (HR) was used for TTP and OS combination across the studies. I^2 statistics was used to measure the heterogeneity of the studies. If the I^2 value was more than 50%, a meta-regression was applied. Then, meta-regression was performed to identify the relative factors for the treatment efficacy of TACE combined with sorafenib. Meta-regression was performed for TTP only if it was the only outcome with sufficient studies for regression analysis. The variables in meta-regression included patient number, age, sex, Child-Pugh A status, and the ECOG PS 0. The meta-analysis and meta-regression were performed using the Stata 12.0 software. $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Studies Included in Meta-Analysis

The date extraction process and the selection of included studies were shown in Figure 1. Twelve studies with full text were considered of interest for detailed evaluation[13-24]. Of these, five studies which consisted of sorafenib therapy and control arm of no sorafenib therapy were eligible for meta-analysis[13-17]. The baseline description of the included studies was listed in Table I. The median age was 59.5 years in the TACE + sorafenib group (n = 948). When only the studies included in meta-analysis were analyzed, the median age was 64.0 years for patients in the TACE + sorafenib group (n = 400) and 61.7 years in the control group (n = 499). Eight and ten studies enrolled patients with HBV-related HCC and HCV-related HCC, respectively. No infection related HCC were enrolled in ten studies. Twelve, eleven and eleven studies reported the severity of liver disease using the Child-Pugh classification system, BCLC and ECOG PS, respectively. All patients had intermediate stage HCC (Child-Pugh class A or B) and most of patients had BCLC had BCLC stage B or C that was not amenable to surgery therapy. The major of ECOG PS were 0 and 1, and no patient had a score greater than 4.

Treatment Regimens

All the included studies used conventional TACE. TACE was performed by injecting chemotherapeutic agents mixed with oil into tumor-feeding artery in nine studies, and was per-

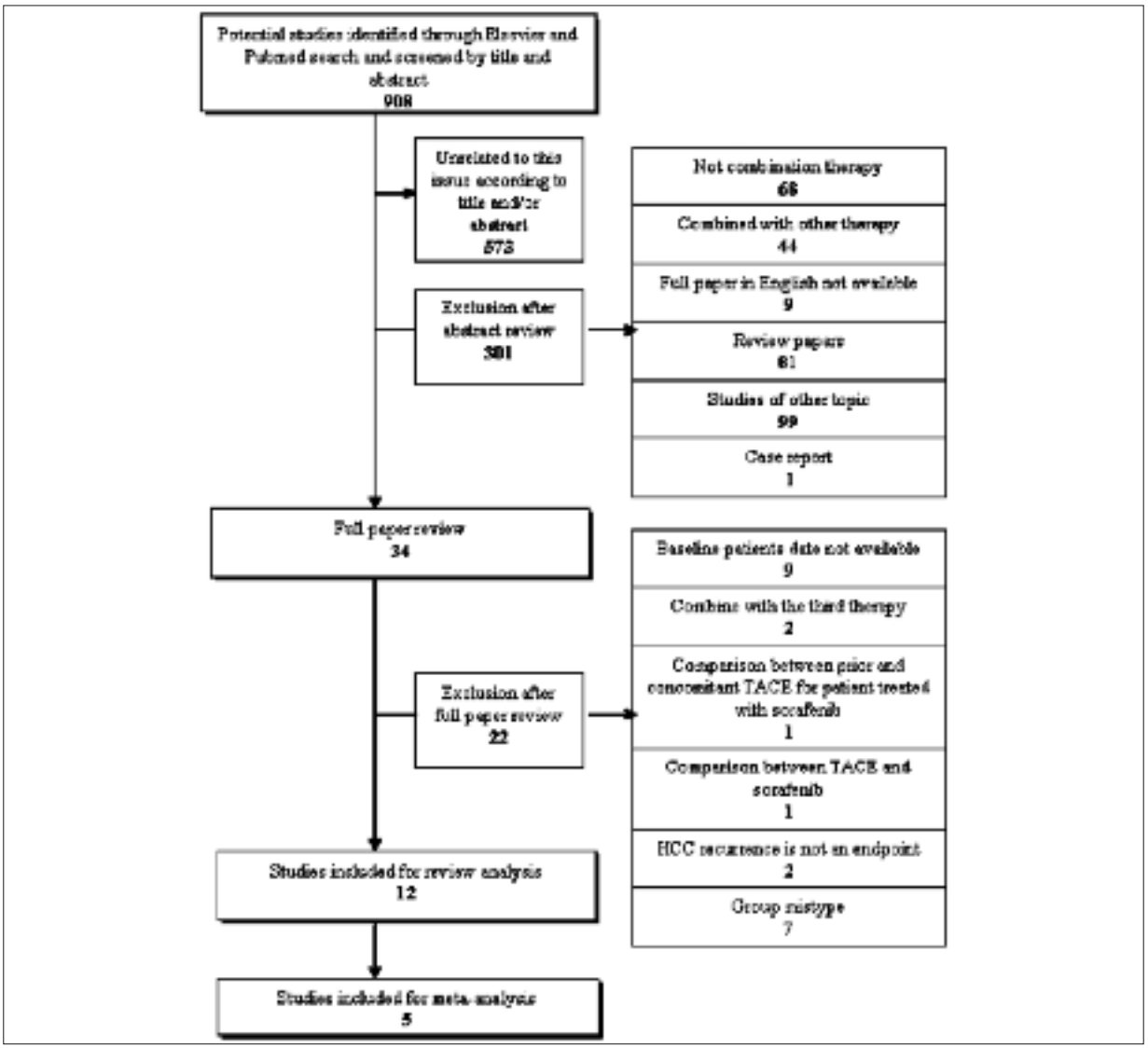

Figure 1. Flow chart of the selection of the studies for meta-analysis.

formed using drug-eluting beads in three studies[15,23,24]. Sorafenib was given continuously until the occurrence of adverse events or tumor progression in eleven studies.

Treatment Efficacy

The outcome characteristics were listed in Table II. Median TTP time, median OS time and median PFS time was reported in seven, six and two studies, respectively.

Meta-analysis of TTP indicated that when the data from all studies[13,14,17] were incorporated, the overall lnHR was 0.75 (95% CI: 0.48-1.03). Moreover, the difference was statistically significant (p = 0.003) with significant heterogeneity (I^2 = 82.7%) (Figure 2A). When the data from two randomized controlled trial (RCT) studies[13,41] were incorporated, the overall lnHR was 0.99 (95% CI: 0.149-1.837), with significant difference and high heterogeneity (p = 0.009, I^2 = 85.4%). When each of the two RCT studies and prospective non-RCT study were incorporated, respectively, the overall lnHR was 0.74 (95% CI: 0.48-1.00) with no difference (p = 0.08) and moderate heterogeneity (I^2 = 67.4%)[13,17], and 0.96 (95% CI: -0.50-2.41) with significant difference and heterogeneity (p = 0.001, I^2 = 91.1%), respectively[14,17].

When the data from all studies[13,15,17] were incorporated, the overall lnHR for OS was 0.76 (95% CI: 0.47-1.05), indicating 24% hazard reduction in

Table I. Baseline characteristic of included studies and patients.

Author (year)	Study type	Group	Patient no.	Etiology	Age	Male (%)	Tumor size (cm)	Multiple tumors (%)	Child-Pugh (%)	Cirrhosis (%)	BCLC Stage (%)	ECOG PS (%)	Treatment characteristics
Kudo (2011) [13]	RCT	S	229	Alcohol/ HBV/HCV	69.0	76.0	N/A	N/A	A = 100	69.4	N/A	0 = 87.8 1 = 12.2	TACE: conventional TACE Sorafenib or placebo were started 1-3 months after TACE and continued until progression, toxicity, or withdrawal of consent
		Con	229		70.0	73.4	N/A	N/A	A = 100	67.2	N/A	0 = 88.2 1 = 12.2	
Sansonno (2012) [14]	RCT	S	31	HCV	73.0 ± 4.0	58.1	7.36 ± 2.22	48.4	A = 100	100.0	B = 100	0 = 86.0 1 = 24.0	TACE: conventional TACE Sorafenib or placebo were given 30 days after TACE, and were stopped following tumor progression
		Con	31		72.8 ± 6.4	61.3	6.94 ± 3.34	41.9	A = 100	100.0	B = 100	0 = 77.0 1 = 23.0	
Muhammad (2013) [15]	CS	S	13	Alcohol/ HCV/ Non-alcohol/ Non-HCV	61.4 ± 7.5	100.0	4	N/A	A/B	100.0	A = 46.1 B = 15.4 C = 38.5	N/A	TACE: conventional TACE Sorafenib was started with 200 mg bid p.o. and increased to 400 mg BID, continued till adverse events
		Con	30		59.2 ± 7.4	100.0	3.1	N/A	A/B	100.0	A = 73.3 B = 26.7 C = 0	N/A	
Qu (2012) [16]	RCT	S	45	HBV/No infection	51.0 ± 11.7	91.1	N/A	35.56	A = 73.3 B = 26.7	N/A	A = 0 B = 35.6 C = 64.4	0 = 95.6 1 = 4.4	TACE: conventional TACE Sorafenib was given with 200 mg tablet twice daily after TACE and adjustment were decided according to adverse enents
		Con	45		49.0 ± 11.0	91.1	N/A	40.00	A = 77.8 B = 22.2	N/A	A = 0 B = 37.8 C = 62.2	0 = 91.1 1 = 8.9	

Table continued

Table I *(Continued)*. Baseline characteristic of included studies and patients.

Author (year)	Study type	Group	Patient no.	Etiology	Age	Male (%)	Tumor size (cm)	Multiple tumors (%)	Child-Pugh (%)	Cirrhosis (%)	BCLC Stage (%)	ECOG PS (%)	Treatment characteristics
Bai (2013) [17]	Prospective non-RCT	S	82	HBV/ HCV/ No infection	54.0 ± 13.0	89.0	N/A	58.5	A = 76.8 B = 23.2	N/A	A = 0 B = 23.2 C = 76.8	0 = 36.6 1 = 46.4 2 = 14.6 3 = 1.2 4 = 1.2	TACE: conventional TACE Sorafenib was initiated at 400 mg twice daily within 14 days after TACE, dose modified was based on the presence of toxicities
		Con	164		52.0 ± 12.0	89.0	N/A	45.9	A = 73.4 B = 26.6	N/A	A = 0 B = 36.5 C = 63.5	0 = 38.3 1 = 53.6 2 = 8 3 = 0 4 = 0	
Zhao (2013) [18]	Multicenter retrospective study	S	222	HBV/ HCV/ Other	51	84	8.7	30	A = 86 B = 14	97	B = 20 C = 80	0 = 44 1 = 50 2 = 6	TACE: conventional TACE Sorafenib was initiated at 400 mg twice daily and continued given till the toxicity
Park (2012) [19]	Single-center, prospective, phase II study	S	50	HBV/ HCV/ Other	61.5	80	3.8	N/A	A = 94 B = 6	N/A	B = 82 C = 18	0 = 44 1 = 56	TACE: conventional TACE Sorafenib was started with 400 mg bid p.o. on day 3 after TACE and was z continued for 24 weeks
Dufour (2010) [20]	Open-label phase I study	S	14	Alcohol/ HCV/NASH/ Unknown	63.5	78	5	50	A = 93 B = 7	N/A	B = 64 C = 36	0 = 93 1 = 7	TACE: conventional TACE Continuous of sorafenib at 200 mg bid to 400 mg bid prior to TACE. Treatment continued until ECOG PS to 4 or unacceptable adverse events or death

Table continued

Table I *(Continued)*. Baseline characteristic of included studies and patients.

Author (year)	Study type	Group	Patient no.	Etiology	Age	Male (%)	Tumor size (cm)	Multiple tumors (%)	Child-Pugh (%)	Cirrhosis (%)	BCLC Stage (%)	ECOG PS (%)	Treatment characteristics
Chung (2012) [21]	Open label, prospective, phase II study	S	165	N/A	57.0	85.5	N/A	N/A	A = 91.6 B = 7.7 Unknow = 0.7	N/A	A = 17.3 B = 80.9 C = 1.9	0 = 82.1 1 = 17.9	TACE: conventional TACE Sorafenib at 400 mg bid was given day 4-day 7 after TACE TACE/sorafenib cycles were repeated every 6-8 weeks, and up to maximum of 6 TACE cycles
Sieghart (2012) [22]	Open label, Single-arm study	S	15	Alcohol/ HBV/HCV/ NASH/AIH	67	86.7	6.9 ± 2.7	60	A = 80 B = 20	N/A	A = 6.7 B = 60.0 C = 33.3	0 = 93.3 2 = 6.7	TACE: conventional TACE Sorafenib continuous at 400 mg bid was started 2 weeks before TACE until the patient withdrew consent, adverse events or death
Pawlik (2011) [23]	Prospective single-center phase II study	S	35	HBV/ HCV/ Alcohol/ Hemochro-motosis/ Cryptogenic cirrhosis/Other	63	74	7.7 ± 4.2	N/A	A = 89 B = 11	N/A	B = 34 C = 64	0 = 46 1 = 54	TACE: drug-eluting bead (DEB) –TACE was performed 1 week after sorafenib Sorafenib continuous at 400 mg bid was started 1 week before TACE and throughout the treatment cycles Patients were treated on a 6-week cycle and the treatment continued until unacceptable toxicities
Cabrera (2011) [24]	Prospective single-center phase II study	S	47	HBV/HCV/ Hemochro-motosis/ Cryptogenic cirrhosis/ NASH/Other	61.21	70.2	N/A	N/A	A = 72.3 B = 27.7	N/A	B = 81 C = 19	0 = 74.5 1 = 22.5	TACE: DEB –TACE Sorafenib continuous at 400 mg bid was started 2-4 weeks before TACE and the treatment continued until unacceptable adverse events or symptomatic progression or death

N/A not available; S sorafenib; Con control; RCT randomized controlled trial; CS cohort study; NASH nonalcoholic steatohepatitis; AIH autoimmune hepatitis.

Table II. Outcome characteristics of included studies and patients.

Author (year)	TTP			OS			PFS	
	Median time (months)	HR (95% CI)	p	Median time (months)	HR (95% CI)	p	HR (95% CI)	p
Kudo (2011) [13]	5.4 3.7	0.87 (0.70-1.09)	0.252	29.7 N/A	1.06 (0.69-1.64)	0.790	N/A	N/A
Sansonno (2012) [14]	9.2 ± 5.8 4.9 ± 3.2	2.5 (1.66-7.56)	< 0.001	N/A N/A	N/A	N/A	N/A	N/A
Muhammad (2013) [15]	N/A N/A	N/A	N/A	20.6 18.3	0.82 (0.38-1.77)	0.61	0.93 (0.45-1.89)	0.83
Qu (2012) [16]	N/A N/A	N/A	N/A	27 17	N/A	0.001	N/A	N/A
Bai (2013) [17]	6.3 4.3	0.60	0.004 (0.422-0.853)	7.5 5.1	0.61	0.009 (0.423-0.884)	N/A	N/A
	Median TTP time (months)			Median OS time (months)			Median PFS time (months)	
Zhao (2013) [18]	8.5 (95% CI 6.4-10.6) a			12 (95% CI 10.1-13.9)			N/A	
Park (2012) [19]	7.1 (95% CI 4.8-7.5)			N/A			N/A	
Dufour (2010) [20]	N/A			N/A			N/A	
Chung (2012) [21]	9.3			N/A			9.0	
Sieghart (2012) [22]	N/A N/A			10.6 (95% CI 5.2-16.0)				
Pawlik (2011) [23]	N/A			N/A			N/A	
Cabrera (2011) [24]	N/A			18.5 (95% CI 16.1-20.9)			N/A	

[a]The data were evaluated in assessable patients. N/A not available; TTP time to progression; OS overall survival; PFS progression-free survival.

mortality with TACE + sorafenib *vs.* TACE alone. However, the difference was not significant (p = 0.147) with slight heterogeneity (I^2 = 47.9%) (Figure 2B). When the data from RCT study[13] and cohort study (CS)[15] were incorporated, the overall lnHR was 0.98 (95%CI: 0.59-1.38), without significant difference and heterogeneity (p = 0.569, I^2 = 0.00%). When the CS[15] and prospective non-RCT[17] were incorporated, the overall lnHR was 0.63 (95% CI: 0.43-0.83), without any evidence of difference and heterogeneity (p = 0.492, I^2 = 0.00%). When the data from RCT study[13] and prospective non-RCT[17] were incorporated, the overall lnHR was 0.78 (95% CI: 0.35-1.21) with no significant difference (p = 0.051) but significant heterogeneity (I^2 = 73.7%).

The meta-regression analysis was performed for TTP only. We tried to put as many covariates into our model as possible. When data from 3 studies were incorporated, we found no significant interaction between any covariates.

Adverse Events

All studies reported the adverse events (AEs) in the patients and all of the AEs were monitored using the National Cancer Institute Common Terminology Criteria for Adversee Events (NCI-CTCAE) (Table III). Most of the AEs were graded to grade 1 or 2. In less common grade 3 or 4, dose reduction or delay was carried out when necessary for patients' safety. Most AEs were hand foot skin reaction (HFSR), alopecia, rash/desquamation, diarrhea, hypertension, fatigue, anorexia, nausea and vomiting. In RCT/CS studies, the incidence of AEs in sorafenib-treated patients was generally higher than control arm patients.

Discussion

TACE has been accepted as the standard care for intermediate HCC[25]. Sorafenib is the only

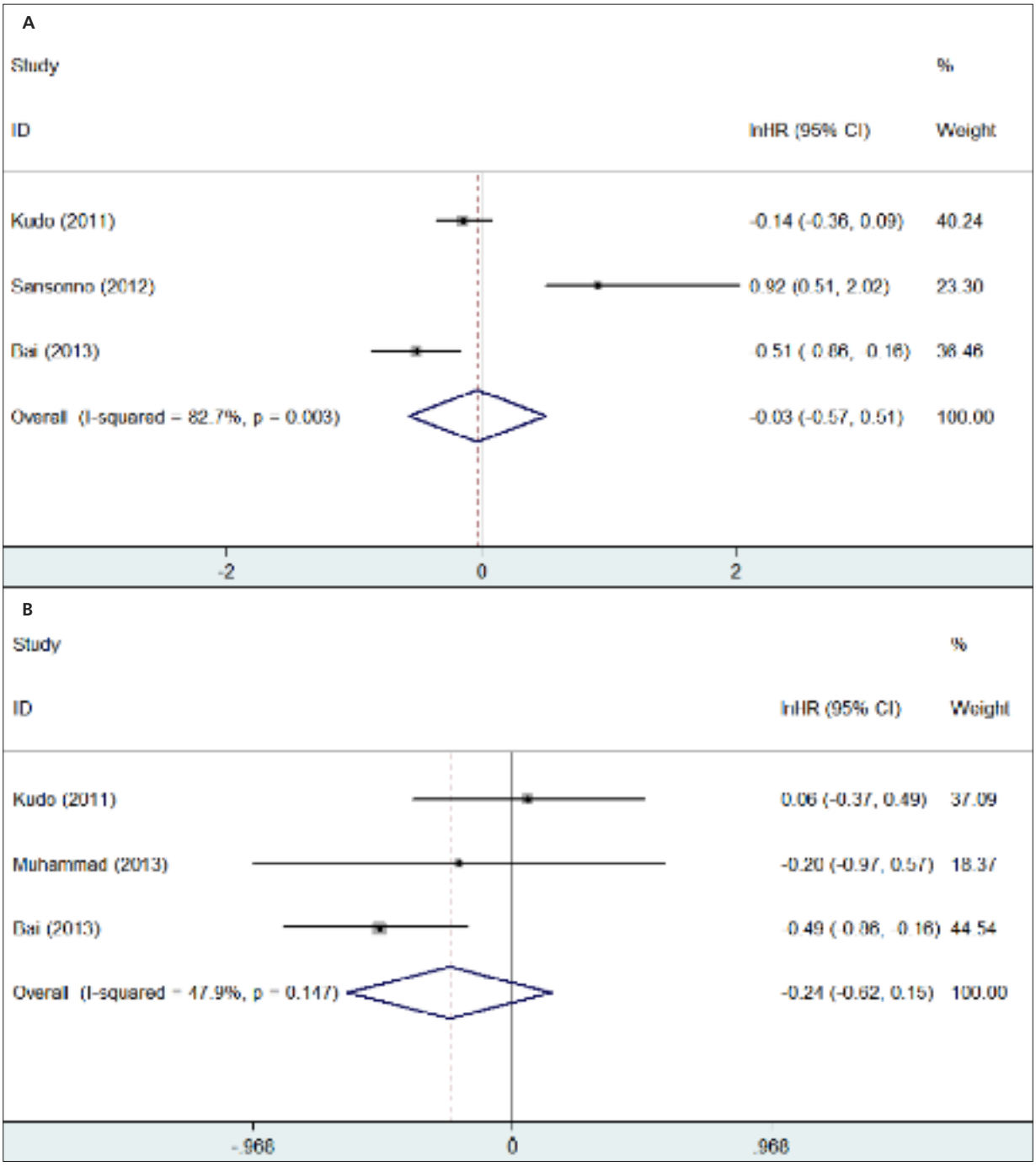

Figure 2. A, Forest plot of TTP of included studies for HCC patients. ***B,*** Forest plot of OS of included studies for HCC patients.

systemic therapy approved by FDA for HCC. However, the sample sizes of many studies are small and their results are heterogeneous. Therefore, it is necessary to evaluate the overall treatment effects with a comprehensive review. In this study our meta-analysis and meta-regression provide comprehensive data of the combination therapy in patients with unresectable HCC.

The current study reviewed the published studies on the combination of TACE and sorafenib for HCC and examined the treatment efficacy by meta-analysis and meta-regression ap-

Table III. Summary of reported adverse events.

Author (year)	Monitor too	Group	HFSR (%)	Elevated lipase (%)	Alopecia (%)	Rash/desquamation (%)	Diarrhoea (%)	Hypertension (%)	Hypophosphatemia (%)	Thrombocytopenia (%)	Fatigue(%)	Hematological event (%)	Nausea, Vomiting (%)	Anorexia (%)	Abdominal pain (%)	Weight loss (%)	Hypoalbuminaemia (%)	Bleeding (%)
Kudo (2011)[13]	NCI-CTCAE	S	82.0	44.0	41.0	40.0	31.0	31.0	28.0	25.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Con	7.0	8.0	3.0	11.0	5.0	7.0	6.0	2.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sansonno (2012) [14]	NCI-Common toxicity criteria	S	10.0	N/A	0.0	20.0	10.0	15.3	N/A	N/A	22.5	13.0	17.5	7.5	N/A	N/A	N/A	N/A
		Con	0.0	N/A	0.0	2.5	7.5	10.0	N/A	N/A	7.5	0.0	7.5	10.0	N/A	N/A	N/A	N/A
Muhammad (2013) [15]	CTCAE	S	2.0	N/A	N/A	N/A	1.0	1.0	N/A	N/A	N/A	N/A	0.0	N/A	1.0	N/A	N/A	N/A
		Con	0.0	N/A	N/A	N/A	0.0	0.0	N/A	N/A	N/A	N/A	3.0	N/A	6.0	N/A	N/A	N/A
Qu (2012) [16]	CTCAE	S	82.2	N/A	46.7	57.7	48.9	55.6	N/A	N/A	55.6	N/A	26.7	31.1	N/A	N/A	N/A	N/A
		Con	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bai (2013) [17]	NCI-CTCAE	S	63.4	N/A	45.1	N/A	36.6	8.5	N/A	N/A	24.4	N/A	7.3	N/A	N/A	N/A	N/A	N/A
		Con	0.0	N/A	0.0	N/A	0.0	0.0	N/A	N/A	0.0	N/A	11.0	N/A	N/A	N/A	N/A	N/A
Zhao (2013) [18]	NCI-CTCAE	S	44.0	N/A	28.0	39.0	50.0	8.0	N/A	N/A	33.0	N/A	3.0	N/A	3.0	5.0	N/A	8.0
Park (2012) [19]	CTCAE	S	74.0	N/A	24.0	12.0	48.0	N/A	N/A	12.0	10.0	N/A	54.0	20.0	64.0	N/A	N/A	N/A
Dufour (2010) [20]	NCI-CTCAE	S	21.0	N/A	21.0	N/A	50.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	28.0	71.0	7.0	N/A
Chung (2012) [21]	NCI-CTCAE	S	N/A	N/A	25.9	N/A	18.4	8.8	N/A	N/A	8.2	N/A	32.6	N/A	35.4	N/A	N/A	N/A
Sieghart (2012) [22]	NCI-CTCAE	S	26.7	N/A	80.0	20.0	46.7	13.3	N/A	60.0	80.0	N/A	53.3	66.7	93.3	86.7	N/A	20.0
Pawlik (2011) [23]	NCI-CTCAE	S[a]	32.0	3.0	3.0	20.0	9.0	12.0	N/A	3.0	52.0	N/A	17.0	11.0	6.0	N/A	N/A	3.0
Cabrera (2011) [24]	NCI-CTCAE	S	51.1	N/A	4.3	N/A	42.6	19.2	2.1	N/A	51.1	N/A	17.0	8.5	23.4	6.4	4.3	12.8

[a]The data were the results of cycle one treatment. N/A not available; HFSR hand-foot skin reaction; S sorafenib; Con control; NCI National Cancer Institute; CTCAE Common Terminology Criteria for Adverse Events.

proaches. First, our study included a total of 12 clinical studies for review. Second, five RCT/CS/ Prospective non-RCT studies were included in meta-analysis and three studies were included in meta-regression for TTP. The meta-analysis indicated the benefit of combination therapy in terms of TTP but not OS. When the data from all studies reporting TTP were analyzed, HR for combination therapy showed significant (p = 0.003). However, when the data from all studies reporting OS were analyzed, HR showed no significant difference (p = 0.147). Furthermore, we found the differences of HR in different study types.

Our meta-regression models only included the studies in which TTP was analyzed. However, all incorporated data had a negative impact on the treatment efficacy of combined therapy. The most significant explanation for this discrepancy is that these studies had other data associated with better TTP after combination therapy. Liu et al[26] evaluated the efficacy of combination therapy as HR of time to progression (TTP) and overall survival (OS) according to the cumulative numbers of TTP and OS reported by individual studies. However, it is important to make the sample statistic of effect size amenable to normal distribution. Therefore, we chose the natural logarithm of HR to explore the temporal trend. Moreover, the results of our analysis were better than theirs. Our conclusion are consistent with recent studies showing that combination therapy was superior to TACE for the prognosis of HCC[27, 28].

Nevertheless, the present work is accompanied by some limitations. First, only five studies were included in meta-analysis and only three studies were included in meta-regression for TTP because other studies are not eligible and necessary details were unavailable. Second, the significance of available data from these studies was not obvious.

Conclusions

Our findings suggest a potential efficacy of the combination of TACE and sorafenib for HCC therapy. Future clinical trials should evaluate the efficacy with larger population and focus on better compliance and the evaluation of OS.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.e1261.
2) Wang JH, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. J Hepatol 2012; 56: 412-418.
3) Andreou A, Vauthey JN, Cherqui D, Zimmitti G, Ribero D, Truty MJ, Wei SH, Curley SA, Laurent A, Poon RT, Belghiti J, Nagorney DM, Aloia TA; International Cooperative Study Group on Hepatocellular Carcinoma. Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. J Gastrointest Surg 2013; 17: 66-77; discussion p. 77.
4) Padhya KT, Marrero JA, Singal AG. Recent advances in the treatment of hepatocellular carcinoma. Curr Opin Gastroenterol 2013; 29: 285-292.
5) Newell P, Toffanin S, Villanueva A, Chiang DY, Minguez B, Cabellos L, Savic R, Hoshida Y, Lim KH, Melgar-Lesmes P, Yea S, Peix J, Deniz K, Fiel MI, Thung S, Alsinet C, Tovar V, Mazzaferro V, Bruix J, Roayaie S, Schwartz M, Friedman SL, Llovet JM. Ras pathway activation in hepatocellular carcinoma and anti-tumoral effect of combined sorafenib and rapamycin in vivo. J Hepatol 2009; 51: 725-733.
6) Zender L, Villanueva A, Tovar V, Sia D, Chiang DY, Llovet JM. Cancer gene discovery in hepatocellular carcinoma. J Hepatol 2010; 52: 921-929.
7) Xie B, Wang DH, Spechler SJ. Sorafenib for treatment of hepatocellular carcinoma: a systematic review. Dig Dis Sci 2012; 57: 1122-1129.
8) Villanueva A, Llovet JM. Targeted therapies for hepatocellular carcinoma. Gastroenterology 2011; 140: 1410-1426.
9) Keefe D, Bowen J, Gibson R, Tan T, Okera M, Stringer A. Noncardiac vascular toxicities of vascular endothelial growth factor inhibitors in advanced cancer: a review. Oncologist 2011; 16: 432-444.
10) Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, LuoR, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, WangJ, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacyand safety of sorafenib in patients in the Asia-Pacificregion with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 25-34.
11) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

12) Gadaleta CD, Ranieri G. Trans-arterial chemoembolization as a therapy for liver tumours: New clinical developments and suggestions for combination with angiogenesis inhibitors. Crit Rev Oncol Hematol 2011; 80: 40-53.

13) Kudo M, Imanaka K, Chida Nobuki, Nakachi K, Tak WY, Takayama T, Yoon JH, Hori T, Kumada H, Hayashi N, Kaneko S, Tsubouchi H, Suh D, Furuse J, Okusaka T, Tanaka K, Matsui O, Wada M, Yamaguchi I, Ohya T, Meinhardt G, Okita K. Phase III study of sorafenib after transarterial chemoembolisation in Jananese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011; 47: 2117-2127.

14) 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: 359-366.

15) Muhammad A, Dhamija M, Vidyarthi G, Amodeo D, Boyd W, Miladinovic B, Kumar A. Comparative effectiveness of traditional chemoembolization with or without sorafenib for hepatocellular carcinoma. World J Hepatol 2013; 5: 364-371.

16) Qu XD, Chen CS, Wang JH, Yan ZP, Chen JM, Gong GQ, Liu QX, Luo JJ, Liu LX, Liu R, Qian S. The efficacy of TACE combined sorafenib in advanced stages hepatocellular carcinoma. BMC Cancer 2012; 12: 263.

17) Bai W, Wang YJ, Zhao Y, Qi XS, Yin ZX, He CY, Li RJ, Wu KC, Xia JL, Fan DM, Han GH. 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.

18) Zhao Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, Liu JS, Li HP, Bai W, Yin ZX, Fan DM, Zhang ZL, Han GH. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. Ann Oncol 2013; 24: 1786-1792.

19) Park JW, Koh YH, Kim HB, Kim HY, An S, Choi JI, Woo SM, Nam BH. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. J Hepatol 2012; 56: 1336-1342.

20) Dufour JF, Hoppe H, Heim MH, Helbling B, Maurhofer O, Szucs-Farkas Z, Kickuth R, Borner M, Candinas D, Saar B. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phaseI study. Oncologist 2010; 15: 1198-1204.

21) Chung YH, Han G, Yoon JH, Yang J, Wang J, Shao GL, Kim BI, Lee TY, Chao Y. Interim analysis of START: study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma trial. Int J Cancer 2013; 132: 2448-2458.

22) Sieghart W, Pinter M, Reisegger M, Müller C, Bassalamah A, Lammer J, Peck-Radosavljevic M. Conventional transarterial chemoembolisation in combination with sorafenib for patients with hepatocellular carcinoma: a pilot study. Eur J Radiol 2012; 22: 1214-1223.

23) Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting Beads for hepatocellular carcinoma. J Clin Oncol 2011; 29: 3960-3967.

24) Cabrera R, Pannu DS, Caridi J, Firpi RJ, Soldevila-Pico C, Morelli G, Clark V, Suman A, George TJ Jr, Nelson DR. The combination of sorafenib with transarterial chemoembolisation for hepatocellular carcinoma. Aliment Pharmacol Ther 2011; 34: 205-213.

25) Boily G, Villeneuve JP, Lacoursière L, Chaudhury P, Couture F, Ouellet JF, Lapointe R, Goulet S, Gervais N. Transarterial embolization therapies for the treatment of hepatocellular carcinoma: CEPO review and clinical recommendations. HPB (Oxford) 2015; 17: 52-65.

26) Liu L, Chen H, Wang M, Zhao Y, Cai G, Qi X, Han G. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. Plos One 2014; 9: e91124.

27) Tu JF, Xu HH, Ying XH, Wang YH, Zhang DK, Tu CY, Ji JS. Comparative study of several microinvasive treatments for large hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2015; 19: 45-53.

28) Kan X, Jing Y, Wan QY, Pan JC, Han M, Yang Y, Zhu M, Wang Q, Liu KH. Sorafenib combined with percutaneous radiofrequency ablation for the treatment of medium-sized hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2015; 19: 247-255.