META-ANALYSIS: THERAPEUTIC EFFECT OF TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION COMBINED WITH COMPOUND KUSHEN INJECTION IN HEPATOCELLULAR CARCINOMA

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Abstract

Compound Kushen Injection (CKI) is *Sophora Flavescens* and *Heterosmilacis Japonicae* extract. Meta-analysis confirmed that CKI plus transcatheter arterial chemoembolization (TACE) is more superior to TACE alone for unresectable hepatocellular carcinoma (UHCC) patients.

Key words: Compound Kushen Injection, Transcatheter arterial chemoembolization, TACE, hepatocellular carcinoma

The list of abbreviations: CKI=Compound Kushen Injection; TACE= transcatheter arterial chemoembolization; UHCC=unresectable hepatocellular carcinoma; WHO=World Health Organization; SD rat=Sprague Dawley Rat; OR=Odds Ratio; CI=Confidence Interval; KPS=Karnofsky Performance Score.

Introduction

Hepatocellular carcinoma is one of the commonest forms of malignancies. Its global morbidity ranks the seventh, while mortality is at fourth position in the world. Statistics from the World Health Organization (WHO, 2008) show that 749,744 cases of hepatocellular carcinoma were diagnosed, of these, 695,726 cases died in 2008. Southern Africa, Southeast Asia and the Mediterranean coast is the high incidence area of hepatocellular carcinoma. Hepatocellular carcinoma has been the second leading cause of death by cancer in China, there were 372,079 deaths in 2008 (Ferlay et al., 2008). However, due to the spread of hepatitis B, the incidence and mortality of hepatocellular carcinoma also show a rising trend (Liaw et al., 1986).

For unresectable hepatocellular carcinoma (UHCC) patients, most of them are at an advanced stage, few meaningful therapeutic options are available (Bruix et al., 2002). TACE is considered as a primary and complementary measure for the treatment of UHCC (Roche et al., 2003; Stuart, 2003; Venook et al., 1990). However, the adverse events of TACE, such as post embolization syndrome, hepatic insufficiency and myelosuppression, are frequent leads to interruption of TACE treatment (Chung et al., 1996). As a result, searching new drugs which can combine with TACE to enhance the therapeutic effects and reduce its adverse events has become a hotspot.

Many clinical trials showed that CKI plus TACE can reduce the adverse reactions and improve quality of life for UHCC (Chen, 2009; Tong, 2010; Zhang et al., 2006; Zhu and Li, 2006). CKI was extracted from the mixture of *Sophora flavescens* and *Heterosmilacis Japonicae* with the mass ratio of 7 than 3. Experimental studies confirmed that CKI has significant killing effect on the tumor cells, such as Hep, H22, LAC and Lewis *in vitro* (Lin et al., 2009). Meanwhile, animal

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experiment showed that CKI can depress the growth of hepatocellular carcinoma and its angiogenesis in SD rat (Sprague Dawley Rat) (Li et al., 2007; Zhu et al., 2011). These results revealed that CKI may enhance the therapeutic effects of TACE. Until now, however, rigorously designed, randomized, large, multi-center, double-blind, controlled trials for UHCC have not been reported.

The purpose of this meta-analysis is to evaluate whether CKI enhances therapeutic effects for UHCC after TACE. It is anticipated that this systematic review will provide evidence-based information for clinical practice.

Materials and Methods
Criteria for Inclusion and Exclusion

The articles were read by two reviewers (Qizhe Sun and Yuan Gao) and studies were selected systematically according to the following criteria: (1) hepatocellular carcinoma patients were confirmed cytologically or pathologically, or diagnosed by CT; (2) trials were described as randomized clinical trials (RCTs); (3) published trials included a treatment group receiving CKI plus TACE and a control group receiving TACE; and (4) the published data of primary interest were tumor response and quality of life for calculation of the odds ratio (OR) at a 95% confidence interval (CI). Trials were excluded if they did not meet the criteria above and included the following: (1) involved animal studies or *in vitro* studies; (2) did not represent primary research (review articles, letters to the editor, etc); or (3) represented duplicate publications of other studies previously identified in our systematic evaluation.

Literature Search Strategy

Retrieval of trials was performed through the Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 5, 2011), CENTRAL (the Cochrane Central Register of Controlled Trials, January 1966 to May 2011), MEDLINE (January 1966 to May 2011), EMBASE (January 1966 to May 2011), CNKI (Chinese National Knowledge Infrastructure, January 1979 to May 2011) and CBMdisk (Chinese Biomedical Database, January 1978 to May 2011). All searches were performed without language limitations to identify all relevant trials. The main search terms were: hepatocellular carcinoma，hepatic tumor, hepatic cancer，liver cancer，or liver tumor and transcatheter arterial chemoembolization, TACE transcatheter arterial embolization or TAE and Compound Kushen Injection, Yan Shu, Kushen, Sophora flavescens or Sophorae. The search results were downloaded to a reference database and screened further.

Outcome Measurements

The main outcome measurements were as follows: (1) Tumor response was evaluated according to the WHO standard for evaluating therapeutic efficacy on solid tumors (Therasse, 2002). Based on the degree of tumor regression, efficacy was evaluated as following: CR (complete response, CT and/or MRI revealed complete clearance of the lesion); PR (partial response, lesion decreased more than 50%); SD (lesion decreased less than 50% or increased less than 25%); PD (size of lesion increased more than 25% after treatment). Tumor responses were defined as CR+PR. (2) Quality of life was evaluated according to the Karnofsky performance score (KPS) (Yates et al., 1980), which was classified as: Improvement (KPS improved $\geq$10 points after treatment)；Stabilization (KPS improved $<$10 points or decreased $<$10 points); Deterioration (KPS decreased $\geq$10 points after treatment). (3) One-year survival. (4) Adverse events were evaluated, based on the WHO criteria for evaluation of acute and subacute toxic and adverse reactions (Miller et al., 1981).

Review Methods
Data extraction

The trials selection and the data extraction were performed independently by two investigators. For conflicts, an agreement was reached by discussion among reviewers. The following information was collected from each study: (1) the information about patients (the number of patients allocated, clinical stage, and KPS); (2) the characteristics of methods (the randomization procedure, concealment of allocation, blinding procedure, withdrawal and reasons, and protection against contamination); (3) The characteristics of interventions (dosage and duration of therapy, TACE course, and any co-interventions; (4) the outcomes (tumor response, quality of life, one-year survival and adverse events).

Quality assessment

Methodological quality was evaluated according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0) (Higgins et al., 2011). The evaluation was performed in the following aspects: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and personnel); (3) detection bias (blinding of outcome assessment); (4) attrition bias (incomplete outcome data); (5) reporting bias (selective reporting); (6) other bias (other sources of bias). The judgement of each term was assigned as: 'Low risk' of bias (the description of methods are adequate and the procedures are correct), 'High risk' of bias (the methods or procedures are improper), or 'Unclear risk' of bias (without description of methods and procedures). The methodological quality evaluation was performed independently by two reviewers, and discrepancies were resolved through discussion.

Statistical method.

Meta-analysis was performed according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al., 2011) using the statistical software RevMan5.1.2 (Update Software Ltd, Oxford, England) provided by the Cochrane Collaboration. Statistical heterogeneity was explored using the x^2 test ($P<0.10$ was considered representative of significant statistical heterogeneity). The random-effects model was used when there was significant statistical heterogeneity ($P<0.10$); otherwise the fixed-effects model was used. For dichotomous variables, OR (Odds Ratio) with 95%CI was calculated. Patients with incomplete or missing data were counted as treatment failures. The sensitivity analysis was performed by comparing the results of two different statistical models (random-effects model and fixed-effects model). Potential publication bias was examined by funnel plot.

Results
Common characteristics

The initial search identified 795 trials for possible inclusion in the review, but all of these trials were reported in Chinese journals. According to the inclusion criteria, 785 trials were excluded as obvious error, non-clinical studies, duplicates, or study objectives different from the aim of this review. Ultimately, 10 trials (Cao et al., 2009; Chen et al., 2006; Chen et al., 2007; Deng et al., 2009; Guan et al., 2006; Huang et al., 2006; Wang and Cheng, 2009; Xu et al., 2010; Yang, 2006; Yu and Kang, 2009) were identified for further study (726 patients), but without a multi-center study. Characteristics of the included trials are listed in Tables 1 and 2.

Table 1: Characteristics of Included Trials

Study	No. Enrolled Patients		Stage	KPS[a]		Treatment vs Control	Outcomes
Author (year)	Treatment	Control		Treatment	Control		
Cao et al., 2009	30	30	II, III	≥60	≥60	TACE-Kushen vs TACE	Tumor response, KPS, and adverse events
Chen et al., 2006	16	14	II, III	>50	>50	TACE-Kushen vs TACE	Tumor response, KPS, and adverse events
Chen et al., 2007	46	40	II, III	≥70	≥70	TACE-Kushen vs TACE	Tumor response, KPS, survival, and adverse events
Deng et al., 2009	20	20	II, III	≥70	≥70	TACE-Kushen vs TACE	Tumor response, KPS, and adverse events
Guan et al., 2006	58	59	II, III	>50	>50	TACE-Kushen vs TACE	Tumor response, KPS, survival, and adverse events
Huang et al., 2006	35	33	II, III	≥50	≥50	TACE-Kushen vs TACE	Tumor response, KPS, and adverse events
Wang et al., 2009	27	30	II, III	≥70	≥70	TACE[b]-Kushen vs TACE	Tumor response, KPS, and survival
Xu et al., 2010	53	53	II, III	—	—	TACE-Kushen vs TACE	Tumor response, KPS, survival, and adverse events
Yang, 2006	33	33	II, III	≥60	≥60	TACE-Kushen vs TACE	Tumor response, KPS, and survival
Yu et al., 2010	48	48	II, III	>60	>60	TACE-Kushen vs TACE	Tumor response, KPS, and adverse events

[a]KPS, Karnofsky Performance Scale; [b]TACE, transcatheter arterial chemoembolization;

Table 2: Compound Kushen Injection and Transcatheter Arterial Chemoembolization Drugs Used in Included Studies

Study	Anticancer Drug	Embolizing			Duration	Compound Kushen Injection	Injection
Author (year)		LP	Agents	Adjuvant Drug	Days	Dosage	Method
Cao et al., 2009	5-Fu, DDP, MMC	Yes	GS particles	MMC	56<D<224	given 20*ml* per time, once daily over 14 days; began in the TACE operation day;	I.v.drip
Chen et al., 2006	5-Fu, DDP, EPI,	Na	Na	Na	63	given 20*ml* per time, once daily over 21 days; begin in the TACE operation day;	I.v.drip
Chen et al., 2007	5-Fu, MMC, EPI,	Yes	Na	Na	84<D<126	given 20*ml* per time, once daily over the whole duration;	I.v.drip
Deng et al., 2009	THP-ADM	Yes	Na	Na	61	given 20*ml* per time, once daily over 14 days; begin in the 2nd day after TACE operation;	I.v.c. infusion
Guan et al., 2006	(5-Fu, DDP, ADM) or (THP-ADM,5-Fu, CBP)	Na	Na	Na	45<D<60	given 20*ml* per time, once daily over the whole duration;	I.v.drip
Huang et al., 2006	5-Fu, ADM, HCPT	Yes	Na	Na	56<D<224	given 15~30*ml* per time, once daily over 10~20 days; begin in the TACE operation day;	I.v.drip
Wang et al., 2009	5-Fu, DDP, ADM	Yes	GS particles	Na	140<D<168	given 20*ml* per time, once daily over 10 days; begin in the TACE operation day;	I.v.drip
Xu et al., 2010	5-Fu, DDP,CF	Yes	Na	THP-ADM or HCPT	60<D<120	given 20*ml* per time, once daily over 15 days; begin in the 3rd day before TACE operation;	I.v.drip
Yang, 2006	DDP, MMC, ADM	Yes	GS particles	Na	40<D<240	given 20*ml* per time, once daily over 20 days; began in the TACE operation day;	I.v.drip
Yu et al., 2010	5-Fu, ADM, HCPT	Yes	GS particles	Na	84	given 20*ml* per time, once daily over 15 days; begin in the TACE operation day;	I.v.drip

5-Fu=fluorouracil, DDP=cisplatin, ADM=Adriamycin, CF=Calcium Folinate, EPI=Epirubicin, MMC=Mitomycin, THP-ADM=pirarubicin hydrochloride, CBP=carboplatin, HCPT=Hydroxycamptothecin, LP=Lipiodol, GS=Gelatin sponge, Na=not described, D=days, I.v.drip=intravenous drip, I.v.c.infusion= intravenous continuous infusion.

In terms of quality, all trials mentioned "randomization," but none stated the generation of a random allocation sequence. No trials described information on allocation concealment and blinding. No trials reported the withdrawals and dropouts. (Figure 1)
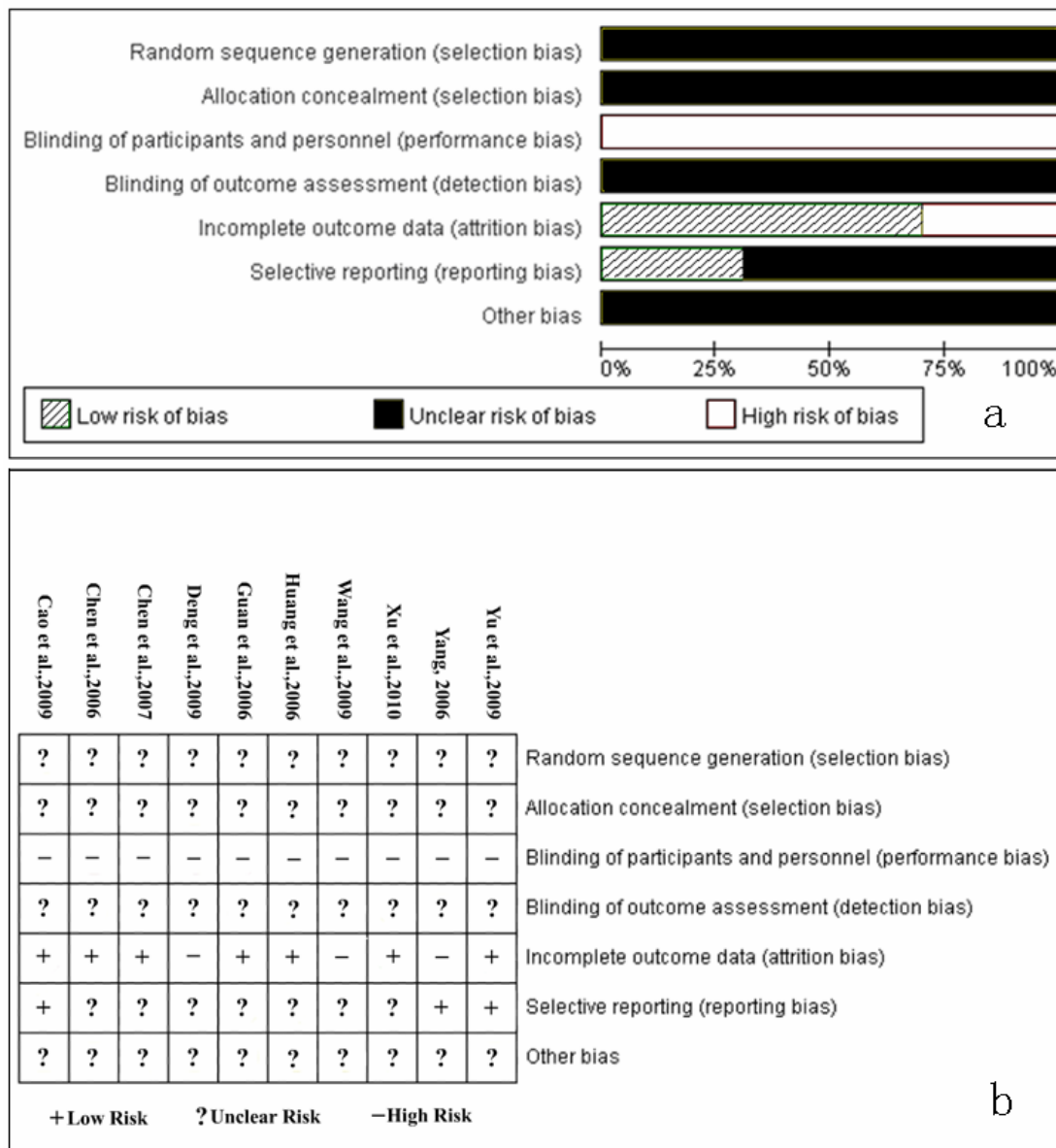

Figure 1: Quality of all included trials

a. Risk of bias percentage graph of all included studies

b. Risk of bias summary of all included studies

Meta-analysis Outcomes

Tumor response

Ten trials (726 patients) (Cao et al., 2009; Chen et al., 2006; Chen et al., 2007; Deng et al., 2009; Guan et al., 2006; Huang et al., 2006; Wang et al., 2009; Xu et al., 2010; Yang, 2006; Yu et al., 2009) were identified with a CR+PR outcome measurement of tumor response. The fixed-effects model was used because of heterogeneity of the results of trials (Heterogeneity: Chi^2=4.74, df=9 (P=0.86); I^2=0%). The pooled analysis showed that compared with TACE alone, CKI plus TACE significantly improved the tumor response (OR=2.01; 95% CI [1.47, 2.74]; P < 0.0001) (Figure 2).

Study or Subgroup	C.K.I.+TACE		TACE		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Cao et al., 2009	17	30	12	30	9.3%	1.96 [0.70, 5.48]	
Chen et al., 2006	6	16	3	14	3.6%	2.20 [0.43, 11.22]	
Chen et al., 2007	25	46	19	40	16.6%	1.32 [0.56, 3.08]	
Deng et al., 2009	2	20	1	20	1.6%	2.11 [0.18, 25.35]	
Guan et al., 2006	34	58	29	59	21.2%	1.47 [0.71, 3.04]	
Huang et al., 2006	12	35	9	33	10.9%	1.39 [0.49, 3.92]	
Wang et al., 2009	21	27	19	30	7.1%	2.03 [0.63, 6.54]	
Xu et al., 2010	37	53	22	53	11.9%	3.26 [1.46, 7.26]	
Yang, 2006	26	33	17	33	6.4%	3.50 [1.19, 10.28]	
Yu et al., 2009	37	48	28	48	11.5%	2.40 [0.99, 5.82]	
Total (95% CI)		**366**		**360**	**100.0%**	**2.01 [1.47, 2.74]**	
Total events	217		159				

Heterogeneity: Chi² = 4.74, df = 9 (P = 0.86); I² = 0%
Test for overall effect: Z = 4.37 (P < 0.0001)

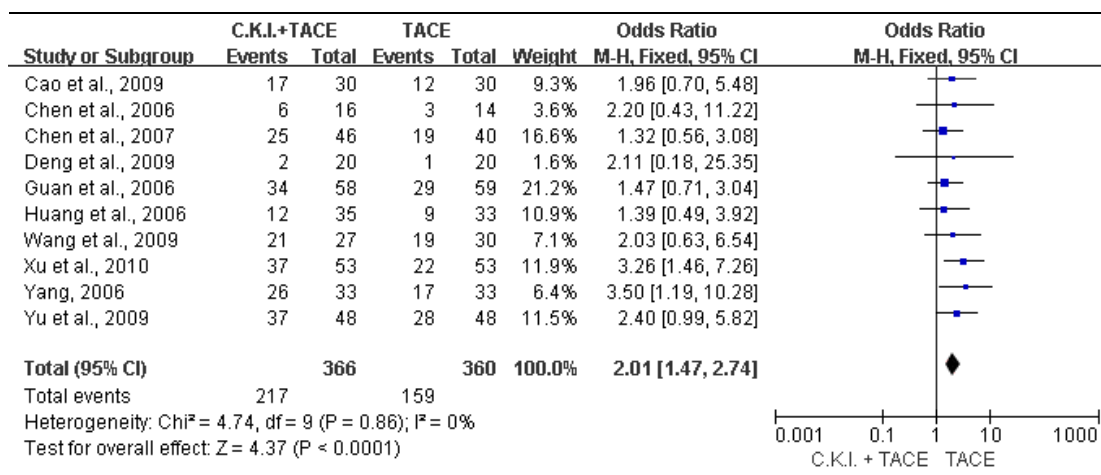0.001 0.1 1 10 1000
C.K.I. + TACE   TACE

Figure 2: Meta-analysis of tumor response.

Compound Kushen Injection (C.K.I.) plus transcatheter arterial chemoembolization (TACE) versus TACE alone for tumor response (CR+PR) of patients with unresectable hepatocellular carcinoma.

Quality of life

There were 9 trials (Cao et al., 2009; Chen et al., 2006; Chen et al., 2007; Guan et al., 2006; Huang et al., 2006; Wang et al., 2009; Xu et al., 2010; Yang, 2006; Yu et al., 2009) contained a KPS improvement of >10 points. The fixed-effects model was used (Heterogeneity: Chi²=5.51, df=8 (P=0.70); I²=0%). The results showed that CKI plus TACE significantly improved KPS (OR=2.47; 95% CI [1.77, 3.44]; P < 0.00001) (Figure 3).

Study or Subgroup	C.K.I.+TACE		TACE		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Cao et al., 2009	23	30	14	30	7.3%	3.76 [1.24, 11.38]	
Chen et al., 2006	5	16	1	14	1.6%	5.91 [0.60, 58.48]	
Chen et al., 2007	18	46	6	40	8.7%	3.64 [1.27, 10.42]	
Guan et al., 2006	30	58	24	59	25.5%	1.56 [0.75, 3.25]	
Huang et al., 2006	23	35	10	33	7.8%	4.41 [1.59, 12.21]	
Wang et al., 2009	8	27	6	30	8.9%	1.68 [0.50, 5.69]	
Xu et al., 2010	16	53	10	53	15.5%	1.86 [0.75, 4.59]	
Yang, 2006	11	33	7	33	10.4%	1.86 [0.62, 5.61]	
Yu et al., 2009	26	48	14	48	14.3%	2.87 [1.24, 6.66]	
Total (95% CI)		**346**		**340**	**100.0%**	**2.47 [1.77, 3.44]**	
Total events	160		92				

Heterogeneity: Chi² = 5.51, df = 8 (P = 0.70); I² = 0%
Test for overall effect: Z = 5.34 (P < 0.00001)

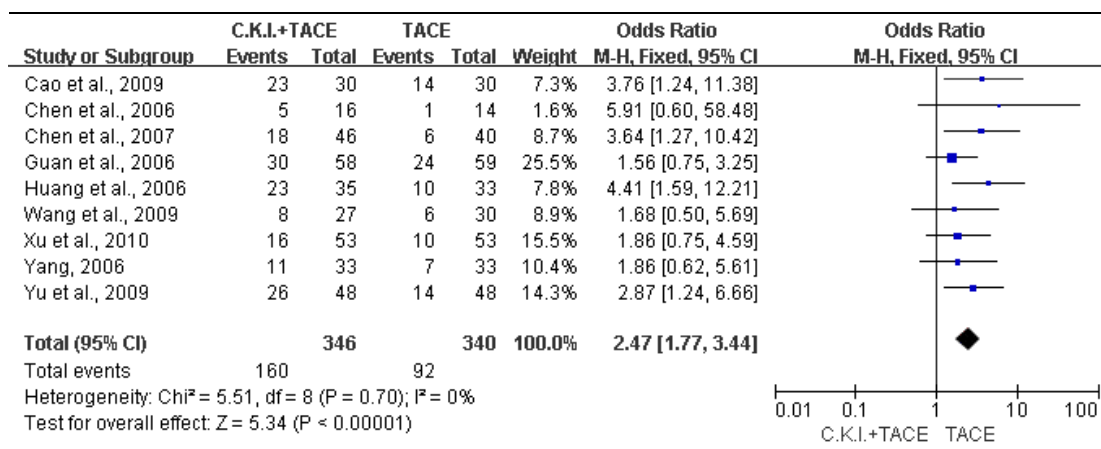0.01 0.1 1 10 100
C.K.I.+TACE   TACE

Figure 3: Meta-analysis of quality of life improvement.

Compound Kushen Injection (C.K.I.) plus transcatheter arterial chemoembolization (TACE) versus TACE alone for KPS (>10 points) of patients with unresectable hepatocellular carcinoma.

One-year survival

Five trials (432 patients) (Chen et al., 2007; Guan et al., 2006; Wang et al., 2009; Xu et al., 2010; Yang, 2006;) were identified with the outcome measurements of one-year survival. The fixed-effects model was used (Heterogeneity: Chi²=1.92, df=4 (P=0.75); I²=0%). The meta-analysis showed that CKI plus TACE significantly improved one-year survival (OR= 2.16; 95% CI [1.45, 3.23]; P=0.0002) (Figure 4).
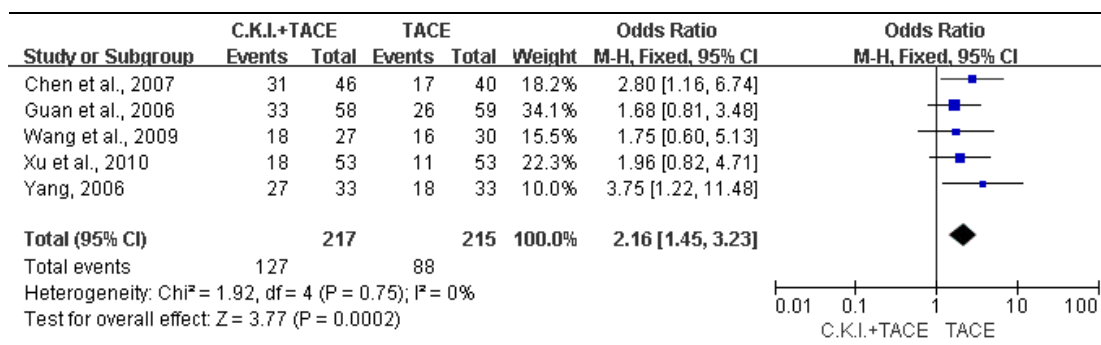
Figure 4: Meta-analysis of one-year survival.

Compound Kushen Injection (C.K.I.) plus transcatheter arterial chemoembolization (TACE) versus TACE alone for one-year survival of patients with unresectable hepatocellular carcinoma.

Adverse Effects

We found 8 trials (Cao et al., 2009; Chen et al., 2006; Chen et al., 2007; Deng et al., 2009; Guan et al., 2006; Huang et al., 2006;   Xu et al., 2010; Yu et al., 2009) mentioned adverse events. All of the eight trials reported that the common symptoms such as abdominal pain, abdominal distension, diarrhea, hepatic insufficiency, and bone marrow depression were found in both groups. These might be due to the complications of TACE. There were six trials (Cao et al., 2009; Chen et al., 2006; Chen et al., 2007; Huang et al., 2006;   Xu et al., 2010; Yu et al., 2009) showed that compared with TACE alone, CKI plus TACE significantly reduced the complications of TACE. In addition, two trials (Deng et al., 2009; Guan et al., 2006) reported that no adverse events attributable to CKI were observed. Therefore, we concluded that the use of CKI has no significant adverse events.

Sensitivity Analysis

Sensitivity analysis was performed by comparing fixed-effects versus random- effects. In the primary analysis, outcome on quality of life was applied to the fixed-effects model (OR=2.47; 95% CI [1.77, 3.44]; P < 0.00001). Therefore, a random-effects model was used to re-analyzed it (OR= 2.45; 95% CI [1.75, 3.43]; P < 0.00001). The results were virtually identical.

Publication Bias

We used the funnel plot to access the publication bias of literatures (Figure 5). The shape of the funnel plots seemed symmetric, and suggesting there was no obvious publication bias.

DISCUSSION

Experimental studies Show CKI can significantly enhance the apoptosis rates of HepG2 cells and inhibit its transition from G2 phase to M phase *in vitro*. Therefore, the proliferation of tumor cells, such as HepG2 cells, BEL-7402 cells and SGC-7901 cells could be restrained by CKI. Further Studies show that the expression of tumor metastasis suppressor gene — nm23 could remarkably be promoted by CKI in BEL-7402 cells, meanwhile in contrast, the expression of CD_{44v6} in BEL-7402 cells could be depressed (Li et al., 2006). Based on these data, CKI could be a complementary drug with TACE to inhibit the growth of liver cancer, suppress the tumor metastasis, and improve quality of patients' life for UHCC.
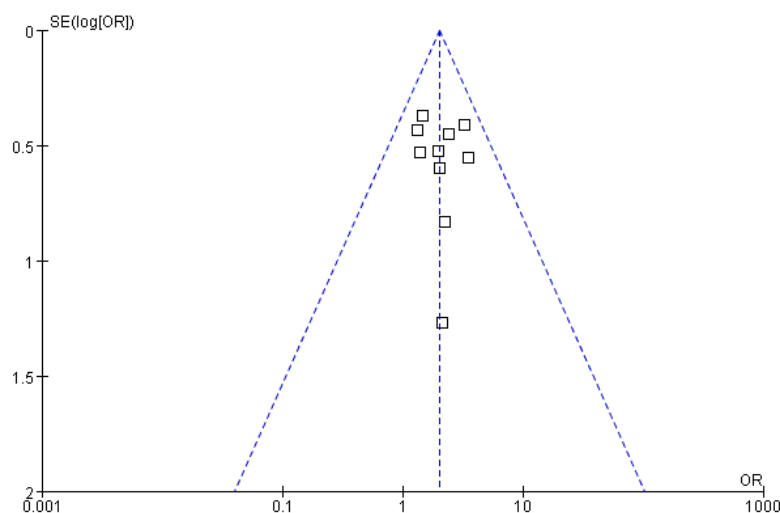
Figure 5: Funnel plot of tumor response (CR+PR).

A graphical display of the logarithm of odds ratio (OR) plotted against OR. The vertical line indicates that there was no publication bias.

The results show that TACE plus CKI seemed superior to TACE alone for UHCC in respect to patients' tumor response, quality of life and one-year survival. Although quality of included literature are low, the results of this study present credible evidence that the administration of CKI plus TACE is worthy of additional study. Hence, larger, longer-term, rigorously designed, multi-center, randomized, double-blind, controlled trials are required to fully assess whether CKI plus TACE is more outstanding than TACE alone.

There are some limitations in this meta-analysis. Due to all literatures we found were of poor methodological quality, the definite conclusions could not be made base on our data. All included trials mentioned "randomized," but all of them did not describe the information of randomization sequence generation, allocation concealment, and blinding. All included literatures did not report the withdrawals and dropouts. We found that the number of patients in experimental group and control group has no change before and after treatment. So it is possible that there are no withdrawals and dropouts happened. However, the evaluation of one-year survival should be interpreted with caution.

Acknowledgments

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