REVIEW

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Thalidomide Combined with Transcatheter Arterial Chemoembolization (TACE) for Intermediate or Advanced Hepatocellular Carcinoma: A Systematic Review and GRADE Approach

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Abstract

Objective: According to current guidelines, there is no clear second-line treatment for advanced liver cancer. In practice, clinicians have attempted to use thalidomide(TLD) combined with transcatheter arterial chemoembolization (TACE) for treating liver cancer. This study aims to assess the clinical efficacy and safety of TLD combined with TACE in patients with intermediate or advanced hepatocellular carcinoma. **Methods:** Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), database of ClinicalTrials.gov, CBM, CNKI, VIP and Wanfang database were searched for eligible studies. Criteria for inclusion in our meta-analysis included a study that patients diagnosed with intermediate or advanced HCC, the use of TACE plus TLD or its derivatives, and the availability of outcome data for survival. A meta-analysis was conducted to summarize the evidences of randomized controlled trials (RCTs). And finally, the GRADE approach was used to assess the quality of these evidences. **Results:** Twelve RCTs involving 894 Hepatocellular Carcinoma (HCC) patients were included. The meta-analysis results showed that TACE plus TLD was significantly superior than TACE alone in terms of 12-month survival rate (OR=2.55, 95% CI:1.78-3.64, P<0.01), 24-month survival rate (OR=2.95, 95% CI:1.96-4.44, P<0.01), 36-month survival rate (OR=2.95, 95% CI:1.41-6.19, P<0.004), progression-free survival (PFS) (MD=2.23, 95% CI:1.19-3.28 , P<0.001), objective response rate (OR=1.84, 95% CI:1.34-2.52, P<0.0001), and disease control rate (OR=2.68, 95% CI:1.80-3.99). Subgroup analysis demonstrated no differences across related outcomes. Sensitivity analyses showed no important differences in the estimates of effects. Quality of evidence for all outcomes was rated moderate to very low after applying GRADE approach. **Conclusions:** Current evidence seemed to support the suggestion that TACE plus TLD as the second line treatment for patients with intermediate or advanced HCC. However, this finding is not definitive due to the poor quality of included studies, more carefully designed and conducted RCTs are warranted to confirm above conclusions.

Keywords: Carcinoma- hepatocellular- chemoembolization- Thalidomide- systematic review

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Introduction

Liver cancer is the mostly common cause of death worldwide, and it was estimated to be responsible for nearly 745,000 deaths in Globocan 2012 (Ferlay et al., 2015). The overall mortality to incidence rate reaches to 0.95 (Omata et al., 2017). In China, the number of deaths was estimated nearly 422,100 in 2015 (Chen et al., 2016). The age-standardized 5-year relative survival in China only amounted to 10.1%, of those, hepatocellular carcinoma (HCC) was the leading histologic subtype (Zeng et al., 2015; Zhang et al., 2015). Transarterial chemoembolization (TACE) is one of the most commonly used treatments for unresectable HCC (Forner et al., 2010). Current Guidelines, such as European Association for Study of the Liver (EASL) (Liver, 2012), American Association for the Study of Liver Diseases (AASLD) (Chalasani et al., 2012) and Asian Pacific Association for the Study of The Liver (APASL) (Omata et al., 2017) recommend TACE and sorafenib as the standard treatment for intermediate or advanced HCC respectively. Recent studies have demonstrated that TACE is effective for curtailing tumor vasculature and delaying tumor progression in advanced HCC (Llovet et al., 2002; Lo et al., 2002;

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Llovet and Bruix, 2003; Llovet and Bruix, 2008), with preserved liver function and sufficient performance status (Luo et al., 2011). The effectiveness of survival benefit was also demonstrated in a meta-analysis of six RCTs (Llovet et al., 2008a). For patients with advanced HCC, Sorafenib is the only approved agents (Llovet et al., 2008b; Wilhelm et al., 2008; Cheng et al., 2009). However, the diarrhea and hand-foot skin reaction in Sorafenib group were common and more serious than placebo group (Omata et al., 2017). Besides, Sorafenib is too expensive to afford for most patients in developing countries. In practice, clinicians attempt to use TLD to treat patients with advanced HCC. TLD had been intensively investigated as an antiangiogenesis (Hsu et al., 2003). TLD is valuable in early stage small HCC, especially in those with other underlying diseases (Chiou and Wang, 2006), and the salvage therapy of advanced HCC (Wang et al., 2004; Lin et al., 2005; Patt et al., 2010). Some studies showed that a single agent, low-dose TLD had a modest clinical activity (Yau et al., 2007; Pinter et al., 2008). In China, a randomized controlled trial demonstrated that TLD plus TACE had the same effect as Sorafenib combined with TACE (Zheng et al., 2016). Recently, a meta-analysis also indicated that TACE plus TLD had a better clinical efficacy and tolerable adverse events in patients with primary HCC (Cao et al., 2017). Nevertheless, there is still a controversy about its efficacy and safety, another study argued that the combination (TACE+TLD) was unlikely to be pursued for HCC because of its lack of clear therapeutic benefits (Wu et al., 2014).

Regarding to the inconclusive efficacy and safety of TLD for patients with intermediate or advanced HCC as well as the uncertain mechanism of TLD for treating HCC, a systematic review and GRADE approach (The Grading of Recommendations, Assessment, Development and Evaluation, GRADE) (Atkins et al., 2004) was performed to compare the TACE plus TLD with TACE alone for treating patients with intermediate or advanced hepatocellular carcinoma.

Materials and Methods

The protocol was firstly conducted with RevMan 5.3 (Version 5.3 for Windows; Cochrane Collaboration, Oxford, UK), and then, the systematic review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions, and presented based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) (Moher et al., 2015). Next, GRADE approach was carried out to rate the quality of evidence (Guyatt et al., 2008).

Eligibility criteria

Type of studies

We included RCTs either published or unpublished without language restrictions. Conference abstracts, letters, case reports, quasi-randomized trials (Q-RCTs), controlled clinical trials (CCTs) were excluded.

Type of population

Trials that included patients diagnosed with intermediate or advanced HCC were eligible for our study(Yang and Ren, 2000; Bruix and Sherman, 2011; Chalasani et al., 2012; Liver, 2012; Omata et al., 2017). The intermediate stage consisted of Child-pugh A and B patients with large/multifocal HCC and without cancer related symptoms, macro-vascular invasion or extrahepatic spread; the advanced stage consisted of Child-pugh A and B patients with cancer symptoms and/or with vascular invasion or extrahepatic spread.

Patients with poor liver function (Child-pugh C) or secondary or metastatic liver cancer were excluded.

Types of interventions

Treatment with TACE plus TLD or its derivatives verse treatment with TACE alone or TACE plus placebo. Any type, setting, dose, frequency, intensity and/or timing of TLD were eligible for this review. Any protocol of TACE was eligible for this review, too. Trials which investigated combination therapy were also included if the combined agents were same between experimental intervention and comparator groups.

Types of outcome

Primary outcome

survival rate. We planned to assess short term (<6months of treatment), intermediate term (12 months of treatment) and long term (more than 24 months of treatment) outcome measurements, progression-free survival (PFS).

Secondary outcomes

Objective response rate (ORR), disease control rate (DCR) and adverse events. The ORR and DCR were defined as (cases of CR plus PR)/total cases and (cases of CR, PR and SD)/total cases, respectively. Target lesion response(CR, PR and SD) was valued by Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al., 2009) or modified Response Evaluation Criteria in Solid Tumors (mRECIST) (Lencioni and Llovet, 2010). Adverse events were assigned by Common Terminology Criteria for Adverse Events (CTCAE 3.0 or 4.0) (Cancer, 2010).

All outcomes were assigned a value of 1to 9 (7-9,critical; 4-6, important; and 1-3, of limited importance) based on the clinical importance to distinguish (Table1).

Literature search

Electronic Searches

We used electronic search strategies to identify relevant RCTs, reviews and meta-analyses. There were no language or publication year restrictions. We searched the following sources: Medline (OVID), Embase (OVID), the Cochrane Central Register of Controlled Trials (CENTRAL OVID), Chinese Biomedicine Database (CBM), China National Knowledge Infrastructure (CNKI), VIP Information Database (VIP), and Wanfang database. Date of last search was 18 JUNE 2017. We also searched ClinicalTrials.gov to identify additional relevant clinical trials and confirmed mortality data from all eligible published trials.

Search Other Sources

We screened reference list of all obtained literature. Additionally, conference proceedings and dissertation abstracts were also retrieved to identify unpublished studies.

Study selection

Two reviewers (W-J. Y, D-D. W) independently screened the title, abstract or both of every record retrieved. All potentially relevant publications were investigated as full text. Disagreements were resolved by discussion. An adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection is presented (Figure 1).

In the case of duplicate publications of a primary study, we assessed those articles together to maximise data collection. In case of conflicting information the primary publication had priority.

Risk of bias assessment

Risk of bias was assessed by using the Cochrane Collaboration's risk of bias tool (Higgins and Green, 2011; Higgins et al., 2011). The items included random sequence generation(selection bias); allocation concealment (selection bias); blinding of participants, caregivers, outcome assessors and outcome adjudicators(performance bias or detection bias); infrequent missing outcome data (attrition bias); incomplete selective reporting, and other bias. Two reviewers (W-J. Y, D-D. W) independently assessed each included trial. Disagreements were resolved by discussion, if necessary, by consultation of a third reviewer (D-Y. K).

Data extraction

For studies that fulfilled the inclusion criteria, Two reviewers (W-J. Y, D-D. W) independently extracted relevant patients' characteristics (age, sex, degree of HCC) and intervention characteristics (such as type, dose, frequency) using a pre-developed form. Disagreements were resolved by discussion or, if necessary, by consultation of a third reviewer (D-Y. K). Any relevant missing information on the trial was sought from the original authors of the publication.

Data Synthesis and Statistical Analysis

We did meta-analysis by using the Review Manager (5.3.3). For dichotomous data, the pooled odd ratio (OR) were calculated with 95% confidence interval (CI). Peto's method was used if necessary. For continuous data, overall treatment effect size was calculated by using mean difference (MD) with its 95% CI or standardized mean differences (SMD) with its 95% CI. The significance of the pooled analysis was assessed by the Z-test. $P < 0.05$ was considered statistically significance (Higgins and Green, 2011).

Heterogeneity was assessed by Cochrane's χ^2 test and the I^2 statistic. If $P<0.1$ or $I^2>50\%$. It was considered significant, then the random-effects model was used. Otherwise, a fixed-effects model was used. Subgroup analyses were used to investigate heterogeneous results, or to explain the potential influence of clinical characteristics (such as particular patient groups or types of intervention) on clinical effects (Higgins and Green, 2011).

We also conducted sensitivity analyses to examine the influence of using alternative effect measures (odds ratio vs relative risk), pooling methods (Peto vs Mantel-Hanszel) and statistical models (fixed effects versus random effects). Zero counts (no events) were replaced by fixed value (typically 0.5) with M-H method versus excluding such trials with M-H method (Higgins and Green, 2011).

GRADE approach was used to rate the quality of evidence for each outcome, and the process of GRADE approach was performed by two reviewers (W-J Y and D-D W) independently. The quality of evidence for each outcome was downgraded by 5 primary domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and was eventually categorized into 4 levels (high, moderate, low, and very low) (G et al., 2011).

Results

Study selection

Our initial search yielded 521 citations, and an updated search yielded an additional 2 citations. Common reasons for exclusion of citations were non-randomized controlled trial and investigation of a non-relevant question. Finally, This review examined 12 RCTs (Guo et al., 2007; Liu et al., 2007; Lin et al., 2009; Su et al., 2009; Wang et al., 2009; Yuan et al., 2009; Wang, 2010; Jang et al., 2011; Shan et al., 2011; Pan et al., 2013; Lu et al., 2014; He et al., 2015) involving 894 people randomized to either TACE or TACE plus TLD. More details were presented in Figure 1.

Study characteristics

All 12 included studies had a single centre, parallel-group design. All trials were performed in China and published in Chinese. The number of participants ranged from 32 to 130. The characteristics of included studies were presented in Table 2.

Assessment of Risk of Bias in Included Studies

The risk of bias of the included trials was considered high. Most of included RCTs only reported "randomly assigned" without details of sequence generation and allocation sequence concealment. Meanwhile, most of the studies did not report the method of blinding, that means potential risk of selection bias may be happening. Six studies were judged ''high risk'' on the item of selective reporting, as their primary outcomes was not prespecified. All of included studies were judged

Table1. Rating Scale for Outcome

Importance	Measure
Critical	survival rate
	PFS
Important	ORR, DCR
	adverse effects
Not important	None

Table 2. Characteristics of 12 Included Trials

Studies	Number of participants		Age (mean ± SD/range, y)		Sex (male)		Stage of HCC (Basis)	Mentioned interm diate or advanced HCC in title?	Funding
	Experiment	Control	Experiment	Control	Experiment	Control			
Xiaobing Yuan 2009	18	21	56.18 (38-75)	56.85 (35-75)	14	17	Stage II, III (Clinical stage, China)	YES	YES
Weimin Wang 2009	21	26	42±10.6	45 ±11.9	12	18	Stage II, III (Clinical stage, China)	YES	NR
Fei Wang 2010	38	34	15-70		48		NR	YES	NR
Xiaoqin Su 2009	37	35	45.7 (31-85)		50		NR	YES	NR
Yan Shang 2011	60	60	31-74		39	30	Stage II, III (TNM)	YES	NR
Xiangdong Lu 2014	30	30	26-77		41		NR	YES	NR
Xiufang Liu 2007	40	58	36-70		62		Stage II, III (Clinical stage, China)	YES	NR
Yunxiao Lin 2010	70	62	31-77	30-76	51	43	Stage II, III (Clinical stage, China)	YES	NR
Haiying Jang 2011	50	50	32-72		50	50	NR	YES	YES
Jianming He 2015	34	34	32-78		34	34	Stage B, C (BCLC)	NO	NR
Peng Guo 2007	15	17	33-66		20		NR	YES	NR
Jiqun Pan 2013	27	27	36-75		38		NR	YES	YES

Studies	Major Intervention strategy(Details)			Major Control strategy
	TACE	TLD	Others	
xiaobing yuan 2009	Epirubicin 60 mg/m^2, camptothecin 20 mg/m^2, 5-Fluorouracil 600mg/m^2, lipiodol embolizatim.	200 mg per day as the starting dose and last 2 weeks,escalated in 200-mg steps every 2 weeks, then 800mg daily on day 56, as tolerated.	NR	The clinical treatment measures exclude TLD that are the same as the intervention group.
Weimin wang 2009	Epirubicin 60 mg/m^2, camptothecin 20 mg/m^2, 5-Fluorouracil 600 mg/m^2, lipiodol embolizatim, Gelfoam embolizatim. if necessary.	200 mg per day as the starting dose,escalated in 100-mg steps every days, then 1000mg daily on day 16, as tolerated.	NR	
Fei wang 2010	Seldinger technic, oxaliplatin 100mg, 5% glucose injection 200ml and 0.9% sodium chloride injection as perfusion therapy. Then doxorubicin 20mg. Iopromide mixed with lipiodol for embolizatim.	100 mg per day as the starting dose, then 200 mg per day on day 8, for 1 year or or until HCC progresses.	NR	
Xiaoqin Su 2009	Seldinger technic, 5-Fluorouracil 0.75-1.0 g, cisplatin 40-60 mg or epirubicin 50 mg, mitomycin 10-16mg, lipiodol embolizatim. Gelfoam embolizatim. if necessary.	100 mg per day as the starting dose, escalated in 50-mg steps every week, then 400mg daily on day 49, as tolerated.	NR	
Yan Shang 2011	Seldinger technic, oxaliplatin 150 mg, camptothecin 10 mg, epirubicin50mg, then epirubicin 5-20 mg mixed with lipiodol for embolism.	100 mg per day as the starting dose, 200mg per day at the second week, then 250mg daily on day 22, for 6 months or until HCC progresses.		
Xiangdong Lu 2014	5-Fluorouracil 0.75-1.0 g, cisplatin 80-100 mg, epirubicin 80-120 mg, lipiodol embolizatim.	100 mg per day as the starting dose, 200 mg daily on day 8, for one year or until HCC progresses.	NR	

NR, not reported

‘‘unclear’’ on the item of other bias (Table3.)

Primary outcomes

6-month survival rates. Two RCTs comprising 171 patients reported 6-months survival rates. Compared with TACE alone, the meta-analysis with a negligible heterogeneity (I^2 = 0%, P = 0.87) failed to show favorable effects of TACE plus TLD (OR=1.95, 95% CI: 0.88-4.34, P =0.10) (Figure 2). A GRADE approach indicated that the quality of evidence supporting this outcome was very low due to high risk of bias, imprecision and publication bias (Table 4).

12-month survival rates. Six RCTs comprising 561 patients reported 12-months survival rates. Compared with TACE alone, there was a statistically significant difference in favour of TACE plus TLD with an odds ratio of 2.55 (95%CI: 1.78-3.64), there was no substantial statistical heterogeneity (I^2 = 19%, P = 0.29) (Figure 2). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate due to high risk of bias (Tables 4).

24-month survival rates. Four RCTs comprising 450 patients reported 24-months survival rates. Compared with TACE alone, the meta-analysis with a low risk of heterogeneity (I^2 = 33%, P = 0.21) indicated that TACE

Table 2. (Continued)

Studies	Major Intervention strategy(Details)			Major Control strategy
	TACE	TLD	Others	
Xiufang Liu 2007	Seldinger technic, Cisplatin 80-100 mg. 5-Fluorouracil 750-1000 mg, Epirubicin 40-50 mg mixed with lipiodol embolizatim.	300 mg per day or until HCC progresses.	NR	The clinical treatment measures exclude TLD that are the same as the intervention group.
Yunxiao Lin 2010	NR	100 mg per day increased to 200 or 300 mg per day, for 18 months or until HCC progresses	NR	
Haiying Jang 2011	Seldinger technic, 5-Fluorouracil 1.2 g, Cisplatin 80-100 mg, Epirubicin 80-120 mg, lipiodol embolizatim.	100 mg per day as the starting dose, 200 mg per day at the second week, for 3 months or until HCC progresses.	NR	
Jianming He 2015	Seldinger technic, Oxaliplatin 130 mg/m^2, arsenic(III) oxide 10mg/m^2, normal saline 200ml for perfusion therapy, then arsenic(III) oxide mixed with lipiodol for embolizatim.	100 mg per day for the first four weeks, then increased to 200 mg per day for 3 months.	All patients taken diaZepatn and ondansetron before TACE	
Peng Guo 2007	5-Fluorouracil, Cisplatin, Doxorubicin.	100 mg per day as the starting dose, escalated in 50-mg steps every week, then 300 mg daily on day 36 as tolerated.	NR	
Jiqun Pan 2013	Seldinger technic, 5-Fluorouracil 0.75-1.0 g, Cisplatin 80-100 mg, Doxorubicin 80-120 mg.	100 mg per day as the starting dose, then increased to 200 mg per day , for 3 months.	NR	

NR, not reported

combined with TLD can improve 24-months survival rates significantly (OR=2.95, 95% CI: 1.96-4.44, P<0.00001) (Figure 2). A GRADE approach indicated that the quality of evidence supporting this outcome was low due to high risk of bias and imprecision (Table 4).

36-month survival rates. Two RCTs involving 218 patients reported 36-months survival rates. Compared with TACE alone, there was significant survival improvement in TACE combined with TLD: OR=2.95 (95% CI: 1.41-6.19), without evidence for statistical heterogeneity (I^2 = 42%, P = 0.19) (Figure 2). A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to high risk of bias and imprecision (Table 4).

PFS. Two RCTs comprising 99 patients reported PFS.

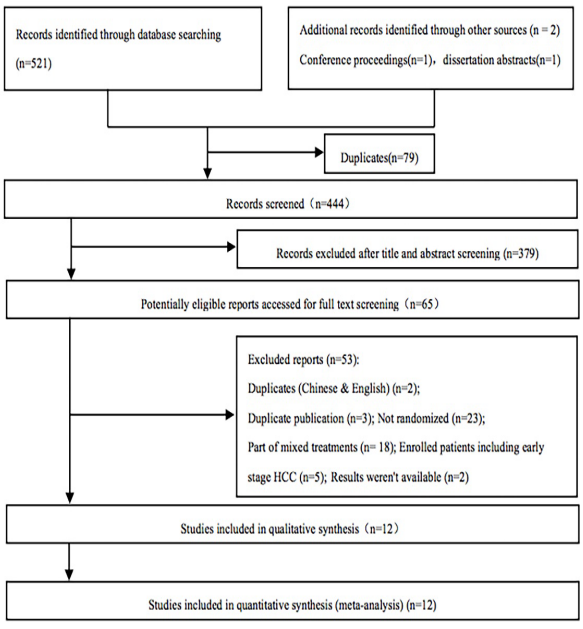

Figure 1. Flow Chart of the Selection Process

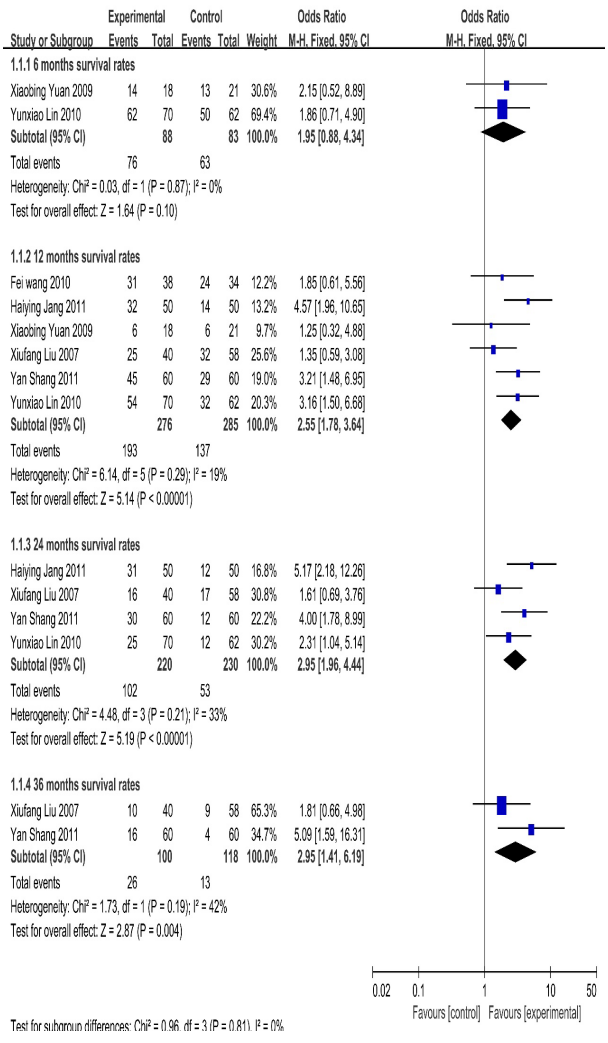

Figure 2. Meta-analyses of Survival Rates (6 months, 12 months, 24 months, 36 months) between TACE Plus TLD Versus TACE alone in Patients with Intermediate or Advanced HCC.

Table 3. Assessment of Risk of Bias in Included Studies

Studies	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of outcome assessment	Incomplete Outcome Data	Selectiv Reporting	Other source of bias
Xiaobing Yuan 2009	unclear	unclear	low	unclear	low	high	unclear
Weimin Wang 2009	unclear	unclear	low	unclear	low	high	unclear
Fei Wang 2008	unclear	unclear	unclear	unclear	low	high	unclear
Xiaoqin Su	unclear	unclear	unclear	unclear	low	low	unclear
Yan Shang 2011	unclear	unclear	unclear	unclear	low	low	unclear
Xiangdong Lu 2014	high	unclear	unclear	unclear	low	high	unclear
Xiufang Liu 2007	unclear	unclear	unclear	unclear	low	unclear	unclear
Yunxiao Lin 2010	unclear	unclear	unclear	unclear	unclear	high	unclear
Haiying Jang 2011	low	unclear	unclear	unclear	low	low	unclear
Jianming He 2015	high	unclear	unclear	unclear	low	low	unclear
Peng Guo 2007	unclear	unclear	unclear	unclear	low	high	unclear
Jiqun Pan 2013	low	unclear	unclear	unclear	low	low	unclear

Compared with TACE alone. The mean difference in endpoint of PFS between TACE alone with TACE plus TLD was statistically significant: MD = 2.24 (95% CI: 1.19-3.28), there was not substantial statistical heterogeneity between studies (I^2 = 0%, P = 0.53) (Figure 3). A GRADE analysis indicated that the quality of evidence supporting this outcome was very low due to high risk of bias, imprecision and publication bias (Table 4).

Secondary outcomes

ORR. Ten RCTs including 723 patients reported ORR, compared with TACE alone, the meta-analysis with a low risk of heterogeneity (I^2 = 0%, P = 0.48) indicated that TACE plus TLD can improve ORR significantly (OR=1.75, 95%CI: 1.28-2.39, P<0.01) (Figure 4). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate due to risk of bias (Table 4).

Subgroup analysis by type of TACE (Based on 5-fluorouracil or Oxaliplatin), showed similar findings of ORR (interaction test P = 0.16; TLD combined with 5-fluorouracil based TACE versus 5-fluorouracil based TACE: 113/225 vs 98/238; OR=1.61, 95%CI: 1.10-2.36, P<0.05; TLD combined with Oxaliplatin based TACE versus Oxaliplatin based TACE: 101/132 vs 75/128; OR=2.44, 95%CI: 1.39-4.27, P<0.05).

DCR. Seven RCTs including 559 patients reported DCR, compared with TACE alone, the meta-analysis without evidence of heterogeneity (I^2 = 0%, P = 0.91) indicated that TACE combined with TLD can improve ORR significantly (OR=2.68, 95%CI: 1.80-3.99, P<0.00001) (Figure 5). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate due to risk of bias (Table 4).

Subgroup analysis by type of TACE (Based on 5-fluorouracil or Oxaliplatin), showed similar finding for DCR (interaction test P = 0.22; TLD combined with 5-fluorouracil based TACE versus 5-fluorouracil based TACE: 127/175 vs 103/196; OR=2.36, 95%CI: 1.52-3.66, P=0.0001; TLD combined with Oxaliplatin based TACE versus Oxaliplatin based TACE: 88/94 vs 72/94; OR=4.57, 95%CI: 1.75-11.95, P=0.002) (Figure 5).

Safety profile. Of the 12 RCTs, 6 trials failed to report anything about adverse events, 4 trials reported incompletely, and the remaining trials reported adverse events in details with a maximum grade of 2. The most common adverse events reported were rash, myelo-suppression, gastrointestinal reaction, and drowsiness. Of those, three trials (Wang et al., 2009; Jang et al., 2011; He et al., 2015) including 215 patients reported rash (31/105 vs 11/110), and myelo-suppression (38/105 vs 11/110). Four trials (Liu et al., 2007; Wang et al., 2009; Jang et al., 2011; He et al., 2015) including 313 patients reported gastrointestinal reaction (95/145 vs 107/168) , and drowsiness (97/145 vs 29/168).

Publication Bias

We minimised the risk of publication bias by performing an extensive search of both electronic sources and additional references. In addition, all 523 citations identified by our electronic search strategies were assessed independently by Two reviewers.

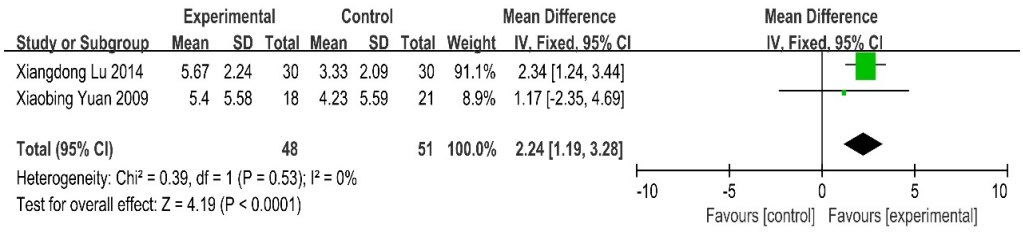

Figure 3. Meta-analyses of PFS between TACE Plus TLD Versus TACE alone in Patients with Intermediate or Advanced HCC

Table 4. Assessment of Quality and Summarizing the Findings with the GRADE Approach

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indire-ctness	Impre-cision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect	Anticipated absolute effects	
							With TACE	With TLD+TACE	(95% CI)	Risk with Contro	Risk difference with Survival Rates (95% CI)
PFS (Better indicated by lower values)											
99 (2 studies)	very seriousa	no serious inconsistency	no serious indirectness	Seriousb	reporting bias strongly suspectedc	⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, imprecision, publication bias	51	48	-		The mean pfs in the intervention groups was 2.23 higher (1.19 to 3.28 higher)
6 months survival rates											
171 (2 studies)	Seriousd	no serious inconsistency	no serious indirectness	Seriouse	reporting bias strongly suspectedc	⊕⊖⊖⊖ VERY LOW[c,d,e] due to risk of bias, imprecision, publication bias	63/83 (75.9%)	76/88 (86.4%)	OR 1.95 (0.88 to 4.34)	Study population 759 per 1000 Moderate 713 per 1000	101 more per 1000 (from 24 fewer to 173 more) 116 more per 1000 (from 27 fewer to 202 more)
12 months survival rates											
561 (6 studies)	Seriousd	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATEd due to risk of bias	137/285 (48.1%)	193/276 (69.9%)	OR 2.55 (1.78 to 3.64)	Study population 481 per 1000 Moderate 500 per 1000	222 more per 1000(from 142 more to 290 more) 218 more per 1000(from 140 more to 284 more)
24 months survival rates											
450 (4 studies)	Seriousd	no serious inconsistency	no serious indirectness	Seriousf	undetected	⊕⊕⊖⊖ LOW[d,f] due to risk of bias, imprecision	53/23 -23%	102/22 (46.4%)	OR 2.95 (1.96 to 4.44)	Study population 230 per 1000 Moderate 220 per 1000	239 more per 1000(from 139 more to 340 more) 234 more per 1000(from 136 more to 336 more)
36 months survival rates											
218 (2 studies)	Seriousd	no serious inconsistency	no serious indirectness	Seriousg	undetected	⊕⊕⊖⊖ LOW[d,g] due to risk of bias, imprecision	13/118 -11%	26/1 -26%	OR 2.95 (1.41 to 6.19)	Study population 110 per 1000 Moderate 111 per 1000	157 more per 1000(from 38 more to 324 more) 158 more per 1000(from 39 more to 325 more)

Table 4. (Continued)

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indire-ctness	Impre-cision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect	Anticipated absolute effects	
							With TACE	With TLD+TACE	(95% CI)	Risk with Contro	Risk difference with Survival Rates (95% CI)
ORR											
723 (10 studies)	Seriousd	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[d] due to risk of bias	177/372 (47.6%)	221/358 (61.7%)	OR 1.85 (1.35 to 2.52)	Study population 476 per 1000	151 more per 1000(from 75 more to 220 more)
										Moderate 482 per 1000	151 more per 1000(from 75 more to 219 more)
DCR											
559 (7 studies)	Seriousd	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ MODERATE[d] due to risk of bias	175/29 (60.3%)	215/269 (79.9%)	OR 2.68 (1.8 to 3.99)	Study population 603 per 1000	200 more per 1000(from 129 more to 255 more)
										Moderate 593 per 1000	203 more per 1000 (from 131 more to 260 more)

[a], The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results; [b], Total population size is less than 400 c It was impossible to check publication bias by test (such as Egger's test) because of limited number of trials for this outcome, funnel plots was assessed by visual assessment. d Most information is from studies at unclear risk of bias. e 95% confidence interval around the best estimate of effect includes no effect, and total (cumulative, n=171) sample size is lower than the calculated optimal information size (OIS, N=97*2). f Total (cumulative, n=450) sample size is lower than the calculated optimal information size (OIS, N=761*2). g Total (cumulative, n=171) sample size is lower than the calculated optimal information size (OIS, N=1802*2).

Table 5. Sensitivity Analyses in Meta-analysis

Outcome	Primary analysis				Alternative effect measure			
	Pooling method	Model	Effect Measure	Point estimate (95%CI)	Pooling method	Model	Effect Measure	Point estimate (95%CI)
6 months	M-H	FE	OR	1.95 (0.88-4.34)	M-H	FE	RR	1.13 (0.98-1.30)
					M-H	RE	OR	1.95 (0.88-4.34)
12Months	M-H	FE	OR	2.55 (1.78-3.64)	M-H	FE	RR	1.44 (1.25-1.66)
					M-H	RE	OR	2.52 (1.68-3.77)
24Months	M-H	FE	OR	2.95 (1.96-4.44)	M-H	FE	RR	2.04 (1.54-2.70)
					M-H	RE	OR	2.95 (1.78-4.90)
36Months	M-H	FE	OR	2.95 (1.41-6.19)	M-H	FE	RR	2.45 (1.31-4.60)
					M-H	RE	OR	2.91 (1.06-8.01)
ORR	M-H	FE	OR	1.84 (1.34-2.52)	M-H	FE	RR	1.29 (1.13-1.47)
					M-H	RE	OR	1.82 (1.33-2.50)
ORR-FU	M-H	FE	OR	1.61 (1.10-2.36)	M-H	FE	RR	1.28 (1.05-1.55)
					M-H	RE	OR	1.61 (1.10-2.36)
ORR-O	M-H	FE	OR	2.44 (1.39-4.27)	M-H	FE	RR	1.30 (1.10-1.54)
					M-H	RE	OR	2.36 (1.05-5.33)
DCR	M-H	FE	OR	2.68 (1.80-3.99)	M-H	FE	RR	1.31 (1.17-1.45)
					M-H	RE	OR	2.65 (1.77-3.95)
DCR-FU	M-H	FE	OR	2.36 (1.52-3.66)	M-H	FE	RR	1.37 (1.16-1.61)
					M-H	RE	OR	2.36 (1.52-3.66)
DCR-O	M-H	FE	OR	4.57 (1.75-11.95)	M-H	FE	RR	1.22 (1.08-1.38)
					M-H	RE	OR	4.58 (1.75-11.96

In addition, we conducted the Egger's test (P=0.894) and funnel plot to assess the risk of publication bias of ORR, and both failed to identify any publication bias (Figure 6).

Sensitivity analyses

We found no unpublished studies. The risk of bias of the included studies was comparable among trials. The robustness of the results was also tested by repeating the analysis using different measures of effects size (MD, SMD, etc.), different statistical models (fixed effects model and random effects model). No significant

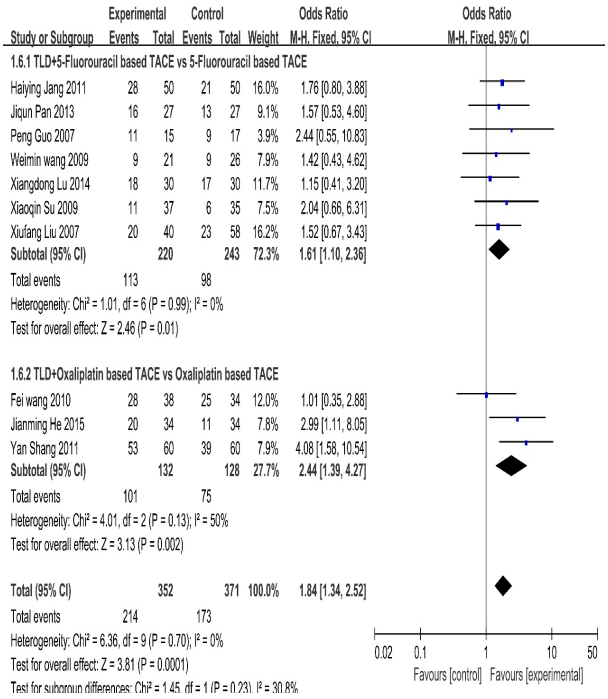

Figure 4. Comparison of ORR between TACE Plus TLD Versus TACE alone in Patients with Intermediate or Advanced HCC

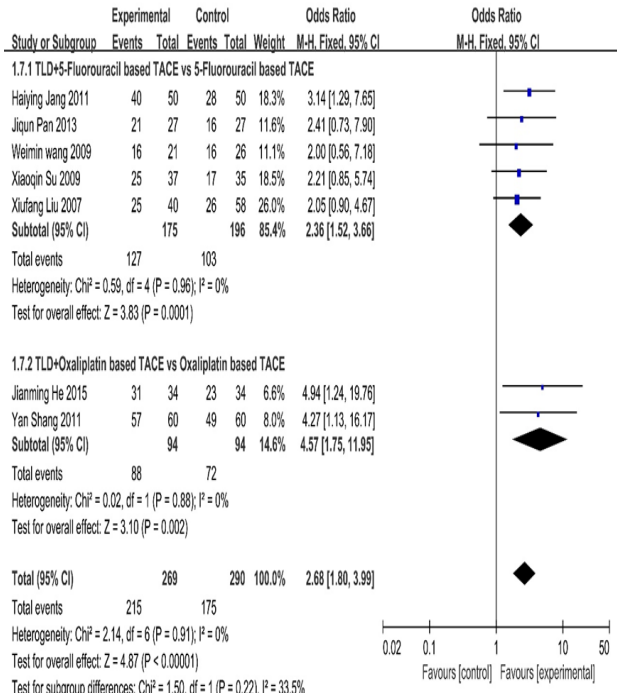

Figure 5. Comparison of DCR between TACE Plus TLD Versus TACE alone in Patients with Intermediate or Advanced HCC

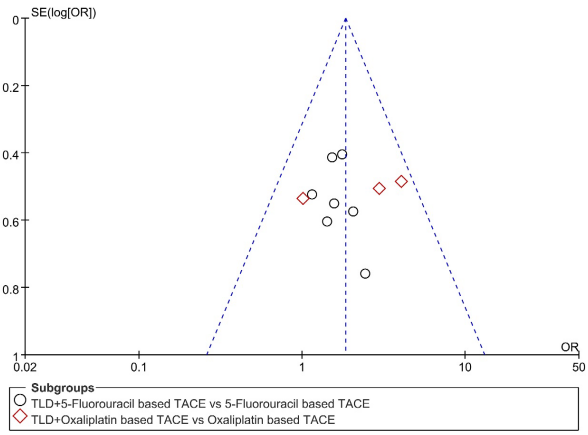

Figure 6. Funnel Plot of ORR in Patients with Intermediate or Advanced HCC Receiving TACE Plus TLD Versus TACE alone.

changes were observed among above analyses (Table 5).

Discussion

Findings and interpretations

This systematic review and meta-analysis included 12 studies comparing the effects of TACE plus TLD to TACE alone in patients with intermediate or advanced hepatocellular carcinoma. Overall, pooling studies resulted in a statistically significant difference in favour of TACE plus TLD, with a slightly longer survival time, higher ORR and DCR. According to those trials reported, the adverse events with a maximum grade of 2 are tolerable. The following GRADE approach demonstrated that the quality of evidence was rated as very low to moderate, which downgraded our confidence to overall evidence from above systematic review.

To date, clinical data implies that combined administration of antiangiogenic and chemo-therapies would yield supreme benefit due to this combination would destroy two separate compartments of cancer cells and endothelial cells (Jain, 2005). Chemo-agents would kill cancer cells by damaging or killing tumor endothelial cells, and/or circulating endothelial cells (Teicher, 1996; Jain, 2005). Antiangiogenic drugs would starve cancer cells directly by inhibiting vessels formation. What's more, antiangiogenic drugs could 'normalize' the abnormal tumor structure. It would be helpful to deliver oxygen and drugs to the targeted cancer cells (Hicklin and Ellis, 2005). The effects of TLD for treating HCC may mainly lie in the following mechanisms: Firstly, due to TLD's antiangiogenic activity, it can change the expression of VEGF, platelet-derived growth factor (PDGF)β, integrins, and reactive oxygen species to inhibit angiogenesis; these molecules were reported to have association with angiogenesis in pathological status (Fillmore, 2000; Stephens and Fillmore, 2000; Feng et al., 2014; Li et al., 2014). Secondly, due to its vascular normalization hypothesis. TLD combined with chemotherapy could remodel tumor vessels and induce tumor reoxygenation. This mechanism is complex and not elucidated up to now (Lebrin et al., 2010; Goel et al., 2011). And finally, regarding its immunomodulatory properties. TLD could regulate the secretion and activity of cytokines, such as tumor necrosis factor (TNF), interferon (IFN) and growth factor, which may contribute to the inhibition of proliferation, angiogenesis and immune system (Ito et al., 2010; Floros and Tarhini, 2015). In conclusion, these mechanisms may enable TLD to be used to treat patients with HCC.

Strengths and limitations

The present study presents some strength. First, an extensive search of both electronic sources and additional references were performed to minimize selection bias. In addition, all 523 citations identified by our electronic search strategies were assessed independently by Two reviewers. Second, we used the GRADE approach to rate an overall body of evidence. This is an important and recommended step in evidence synthesis initiatives (Schünemann et al., 2009), particularly under conditions in which the quality of evidence is either low or unclear. The process of GRADE approach is transparency and reproducible. The GRADE system considers each of the study limitation, such as risk of bias, result inconsistency, indirectness and imprecision. Rating the quality of a body of evidence is key step in translating evidence into clinical practice and recommended for practice guidelines or systematic reviews (Schünemann et al., 2009). According to our knowledge, this is the first GRADE approach combined with SR simultaneously to grade the quality of evidence for the usage of TLD in patients with intermediate or advanced HCC.

By the way, our study also has several limitations. Firstly, all studies included in our review were conducted in China and were published in Chinese journals, although we searched comprehensively without limitation on languages. Regarding to HBV-related HCC makes up 63-70% of the HCC cases in China (Goh et al., 2015; Omata et al., 2017), previous researches had demonstrated that HBV-related HCC and HCV-related HCC have different genetic mechanisms in the regulation of angiogenesis and tumor microenvironment(Mazzanti et al., 1997; Honda et al., 2001; Omata et al., 2017). This leads to downgrade the confidence regard its efficacy and safety for patients outside of China. Therefore, similar studies in other countries are needed to confirm that these results could be replicated in other populations internationally. Secondly, the findings from this study was based on randomized, well-controlled studies in smaller patient populations with more rigid inclusion and exclusion criteria, while translating those RCT findings to everyday clinical practice is often difficult when treating patients who might not fulfill the inclusion criteria of these studies. To complement the results of these randomized studies, increasing emphasis is put on the added value of open-label studies under ''real-world'' conditions that provide clinically relevant additional information about the actual benefits of these therapies in broader patient populations. Thirdly, another seriously concern is about the low quality attribute of current evidences in this study. Small samples are common within all included studies.

Sample size ranges from 32 to 132; In addition, there are significant heterogeneity among clinical characteristics, such as ages, performance status, numbers of participants, intervention characteristics (type, dose, frequency), together with the limited amount of patients further downgrade the confidence of the findings in our study. That means that translating current evidence to practice should be cautiously.

Comparison with other studies

A meta-analysis included 23 RCTS involving 1836 primary HCC patients showed that the combination group of TLD and TACE had superior efficacy of survival rates at 6,12,18,24,36 months, also showed significant benefits about ORR and DCR. The results of their meta-analysis also suggested that TLD treatment significantly improved the quality of life in patients with primary HCC (Cao et al., 2017). In contrast to the study, we enlarged database searching, electronic databases including Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Biomedicine Database (CBM), China National Knowledge Infrastructure (CNKI), VIP Information Database (VIP), and Wanfang database. In order to minimize selection bias, we also searched the reference lists of included RCTs and relevant reviews and meta-analyses. In addition, we limited to include patients with intermediate or advanced HCC. Patients with early stage HCC is recommended to receive the treatment of hepatectomy, transplantation or radiofrequency ablation.

Besides of systematic review and meta-analysis, we also used a GRADE approach synchronously to rate the quality of current evidence. Our study confirmed that patients with intermediate or advanced HCC could get benefits from the combination of TLD and TACE, but the low quality of current evidence downgrade our confidence to those findings. In contrast to our study, the comparable systematic review without applying GRADE demonstrated that all of the selected studies have high quality and the meta-analysis is reliable.

The disagreement can be explained by the different appraisal tools adapted within two studies, the GRADE approach performed in our study includes detailed scrutiny of the potential limitations within a whole body of evidence, considering factors such as risk of bias, result inconsistency, indirectness and imprecision and publication bias. While in the comparable study, only one factor, risk of bias was taken into consideration during critical appraisal process. So far as we know, this is the first study to apply the GRADE approach to evaluate SRs regarding the use of TLD combined with TACE.

In conclusion, TACE plus TLD seem useful and safe in treating patients with intermediate or advanced HCC. However, regard the moderate to very low quality of current evidence, further rigorously designed and multicenter large-scale RCTs are warranted to confirm above conclusions.

Authors' Contributions

Guarantor of the article is Deying Kang. Deying Kang conceived and designed the review. Wenjie Yang, Dandan Wang,conducted literature searches, selected studies, assessed risk of bias, and extracted data. Wenjie Yang, and Dandan Wang, Wen Shu carried out analysis, Wenjie Yang, Litao Huang and Yue Chen applied GRADE, and interpreted results. Wenjie Yang, Deying Kang, and Qi Hong drafted the manuscript. All authors approved the final version of the manuscript.

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