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REVIEW

Transarterial Chemoembolization Plus Sorafenib versus Transarterial Chemoembolization Alone for Advanced Hepatocellular Carcinoma: An Umbrella Review of Meta-Analyses and Systematic Reviews

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Background: Sorafenib is the standard treatment for most cases of advanced hepatocellular carcinoma (HCC), based on Western and Eastern clinical guidelines. Thus, an increasing number of transarterial chemoembolization (TACE) plus sorafenib combination therapies have been used in clinical practice. In addition, several systematic reviews and meta-analyses have explored the efficacy and safety of the combination of TACE and sorafenib. Therefore, we performed an umbrella review to summarize and evaluate these evidence-based studies.

Methods: PubMed, Embase, Cochrane Library, and Web of Science databases were searched up to June 1, 2023. All meta-analyses that evaluated the effect of TACE plus sorafenib on HCC were considered eligible. The quality of the included meta-analyses was evaluated by AMSTAR2 (A Measurement Tool to Assess Systematic Reviews). The quality of evidence per association provided in the meta-analyses was rated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). This study was registered with PROSPERO (Registration ID: CRD42023420417).

Results: We included 12 meta-analyses, including randomized clinical trials, cohort studies, and observational studies. A total of 44 associations with overall survival, survival rate, time to disease progression, overall response rate, disease control rate, and adverse events were evaluated in this umbrella review. The quality of most associations ranged from low to very low, indicating that flaws were significant in the current meta-analyses.

Conclusion: This umbrella review identified beneficial associations between TACE and sorafenib combination therapy in advanced HCC. However, owing to the low certainty of the evidence, clinicians should interpret our results with caution when applying them in clinical practice, and high-quality studies are required in the future to confirm our results.

Keywords: umbrella review, meta-analysis, systematic review, sorafenib, hepatocellular carcinoma, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fourth leading cause of cancer-related death worldwide.[1] The annual incidence of HCC is increasing and is mainly attributed to hepatitis B virus, hepatitis C virus, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and other liver diseases, while some unknown etiologies can also be associated with HCC and cirrhosis.[2–4] Because of the various etiologies and accumulation of genetic changes in HCC, it is a type of heterogeneous cancer, which makes treatment difficult.[5] Surgical, systemic, locoregional, and other potential therapies have been used for the treatment of HCC, and many studies are currently

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underway.[6,7] However, measures have been taken to improve the prognosis of patients with HCC, and the recurrence and mortality rates are still high.[8] In the clinical practice, systemic therapy is recommended treatment for advanced HCC, and clinical studies found that immunotherapy, immunotherapy plus VEGF (or PDGF) inhibitor, and r multi-kinase inhibitor showed benefit when treating advance HCC.[9–12] In addition to systemic therapy, transarterial chemoembolization (TACE), an approach that can embolize the hepatic artery and reduce the blood supply to HCC tissues, is a standard therapy recommended for some BCLC intermediate-stage HCC subgroups with normal liver function.[13–15] In contrast, various anticancer drugs, such as 5-fluorouracil and cisplatin, can be used in TACE, which provides opportunities to control intermediate/advanced-stage HCC.[16,17] Sorafenib, an oral polykinase inhibitor that can inhibit tumor angiogenesis and tumor cell proliferation, has been widely used over past years as the first-line treatment for unresectable advanced HCC.[18] Sorafenib shows antitumor activity in HCC by inhibiting IL-6/STAT3 and other possible pathways.[19] The efficacy and safety of sorafenib/sorafenib-related protocols have been confirmed in several clinical trials, and accordingly, studies focusing on the combination of interventional therapies and sorafenib have found that combination therapy can provide some clinical benefits compared to TACE alone.[20–24]

The impact of the combination of TACE and sorafenib has been broadly examined through many meta-analyses of randomized controlled trials (RCTs) and cohort studies. However, the fact that the combination of TACE and sorafenib is an effective strategy for controlling HCC remains controversial, leading to inconsistent conclusions. Therefore, conducting an umbrella review with an assessment of the overall quality of the existing evidence on this topic is exceedingly important. An umbrella review, a review of review, is a method collecting existing evidence and synthesized higher levels of evidence.[25,26] Therefore, we designed this umbrella review to investigate the pooled effects of TACE and sorafenib combination found in previous meta-analyses.

Methods

Umbrella Review Methods and Registration

Our umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[27] and the protocol was registered with PROSPERO (Registration ID: CRD42023420417).

Search Strategy

A comprehensive search of Embase, Cochrane Library, Web of Science, and PubMed for English-language systematic reviews and meta-analyses of TACE combined with sorafenib versus TACE alone published before June 1, 2023. The search strategy can be found in Table 1.

Selection Criteria

The eligibility criteria were systematic reviews and meta-analyses of observational studies or RCTs measuring the clinical outcomes of TACE plus sorafenib versus TACE alone for advanced HCC. The exclusion criteria were as follows: (1) narrative reviews, primary studies, protocols, theses, and conference papers; (2) studies with statistical errors or other serious flaws; (3) articles that did not assess the outcomes of interest (including but not limited to overall survival, overall response rate, disease control rate, disease progression rate, alpha-fetoprotein, time of disease progression, progression-free rate, and vascular endothelial growth factor); and (4) non-English meta-analysis.

Data Extraction

Two independent reviewers (YHW and JXY) performed the research and data extraction, and disagreements were resolved by a third author (MJD). The following information was extracted from all eligible studies: first author, publication year, number of included studies, study population, and sample size. All the outcomes associated with the included studies were extracted from the original meta-analysis.

Table 1 Index and Keyword Terms Used in the Databases

Database	Index and Keyword Terms
PubMed	(((((Transcatheter arterial chemoembolization[Title/Abstract]) OR (TACE[Title/Abstract])) OR (transarterial chemoembolization[Title/Abstract])) AND ((Sorafenib[MeSH Terms]) OR (nexavar[Title/Abstract]))) AND ((((((((((carcinoma, hepatocellular[MeSH Terms])) OR (hepatocellular carcinoma[Title/Abstract])) OR (hepatomas[Title/Abstract])) OR (liver carcinoma[Title/Abstract])) OR (hepatocarcinoma[Title/Abstract])) OR (liver cell carcinoma[Title/Abstract])) OR (liver cancer [Title/Abstract])) OR (HCC[Title/Abstract]))) AND (meta[Title/Abstract])
Cochrane	ID Search #1 MeSH descriptor: [Sorafenib] explode all trees #2 nexavar #3 #1 OR #2 #4 MeSH descriptor: [carcinoma, hepatocellular] explode all trees #5 hepatocellular carcinoma #6 hepatomas #7 liver carcinoma #8 hepatocarcinoma #9 liver cell carcinoma #10 liver cancer #11 HCC #12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 #13 Transcatheter arterial chemoembolization #14 TACE #15 transarterial chemoembolization #16 #13 OR #14 OR #15 #17 meta #18 #3 AND # 12 AND #16 AND #17
Web of Science	TS= (Transcatheter arterial chemoembolization OR TACE OR transarterial chemoembolization) AND TS= (carcinoma, hepatocellular OR hepatocellular carcinoma OR hepatomas OR hepatocarcinoma OR liver cell carcinoma OR HCC) AND TS= (Sorafenib OR nexavar) AND TS= (meta)
EMBASE	#1. Transcatheter AND arterial AND chemoembolization #2. transarterial AND chemoembolization #3. #1 OR #2 #4. Carcinoma AND hepatocellular #5. hepatocarcinoma #6. ("liver"/exp OR liver) AND cell AND carcinoma #7. #4 OR #5 OR #6 #8. Sorafenib #9. nexavar #10. #8 OR #9 #11. meta #12. #3 AND #7 AND #10 AND #11

Quality Assessment

Two independent reviewers (YHW and LSZ) used AMSTAR2 (A Measurement Tool to Assess Systematic Reviews) to assess the methodological quality of eligible articles. The AMSTAR2 questionnaire uses 16 measures to classify systematic reviews as high, moderate, low, or critically low quality.[28]

Data Synthesis and Analysis

Extraction and analysis were performed using R (R Development Core Team) software version 3.6.1. To assess the certainty of the evidence, the authors used a GRADEproGDT-independent assessment based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Handbook, which considers the following characteristics: study design (observational, randomized clinical trials), inconsistencies between studies (I^2 statistics), imprecision of study results, indirection, publication bias, size effects, and the presence of dose–response gradients.[29–33]

Results

Search Strategy Outcome

A PRISMA flowchart of the literature search process is shown in Figure 1. A preliminary search yielded 1076 articles, of which 568 were duplicates. After removing duplicates using automated tools, we rearranged the abstracts of the remaining studies; 496 articles did not meet the inclusion criteria. Finally, 12 studies[34–45] met the eligibility criteria and were included in the umbrella review, and Table 2 summarizes the characteristics of the included studies.

A description of the selected studies: objectives, number of studies, and most important results is included in Table 2. Li,[34] Zeng,[38] and Xie[36] only included RCTs, whereas the others included both observational studies and RCTs.

Outcome of Quality Assessment

Table 3 shows AMSTAR2 item evaluations for included meta-analyses. Overall, of the 11 papers, eight were of low quality and four were of very low quality. In particular, all included meta-analyses used appropriate methods for statistical method (Q11, 11/12) and a significant publication bias assessment (Q15, 11/12), while none of the review authors provided a list of exclusion studies or justified the exclusion.

The HR, OR, RR, and SMD of the most important outcomes and adverse events are presented in Supplementary Tables S1 and S2.

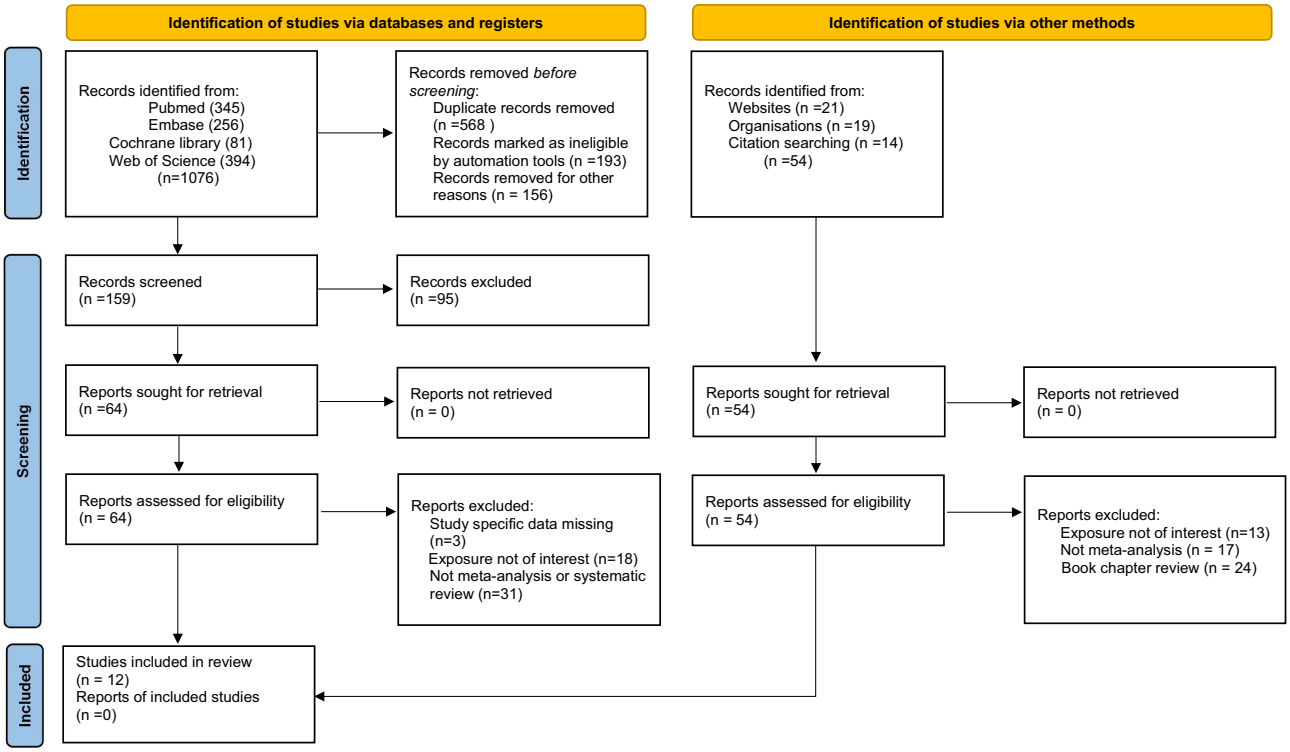

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

Table 2 Description of the Selected Studies: Objectives, Numbers of Studies and Most Important results

Study	Number of Included Studies	Objectives	Results
Li D[34] 2021	23 RCTs	To evaluate the efficacy and safety of sorafenib combined with TACE in the treatment of advanced HCC.	ORR, DCR, TTP, AFP, VEGF, OS and adverse events.
Hu MD[35] 2016	3 RCTs, 1 cohort study and 1 prospective non-RCT	To analyze the efficacy of sorafenib in combination with TACE for HCC.	TTP, OS, treatment efficacy and adverse events.
Xie Y[36] 2020	6 RCTs	To evaluate the efficacy and safety of transcatheter arterial chemoembolization (TACE) plus sorafenib compared with TACE plus placebo for hepatocellular carcinoma (HCC) using meta-analytical techniques.	TTP, 0.5-, 1-, 1.5-, and 2-year survival rates, ORR, DCR.
Cheng[37] 2020	6 RCTs and 25 retrospective studies	To compare the efficacy of three types of palliative therapy for advanced HCC, TACE monotherapy, sorafenib alone and their combination.	OS, TTP, ORR, DPR, 1-year and 2-year survival rates
Zeng J[38] 2016	4 RCTs	To evaluate the efficacy and safety of TACE plus sorafenib versus TACE monotherapy in the early or intermediate stage HCC	TTP, OS, ORR, DCR and adverse events.
Zhang[39] 2014	2 RCTs, 2 propensity score-matched cohort studies, and 2 retrospective cohort studies.	To evaluate the efficacy and safety of the combination therapy of TACE plus sorafenib in patients with intermediate or advanced stage of HCC.	OS, TTP, ORR, PFS and adverse events.
Li L[40] 2018	14 comparative studies (3 RCTs, 4 non-randomized controlled studies and 7 retrospective studies) and 13 non-comparative studies.	Identifying the efficacy of the combination of TACE with sorafenib, which remains controversial despite years of exploration.	OS, TTP, DCR, ORR, PFS and adverse events.
Zhang[41] 2017	Eight retrospective studies	To compare the effectiveness and safety of combination of TACE with sorafenib and TACE alone for HCC with portal vein tumor thrombus.	OS, TTP, tumor objective response and adverse events.
Jin PP[42] 2018	5 RCTs, 2 prospective cohort studies, and 6 retrospective studies	To compare efficacy and safety, as well as regional disparities, between TACE plus sorafenib and TACE alone for HCC.	TTP, OS, and adverse events.
Fu QH[43] 2014	5 RCTs, and 4 non-RCTs	Evaluation of efficacy and safety between sorafenib plus TACE and TACE alone for HCC.	6-month, 1-year and 2-year mortality, PFR, clinical benefit ratio and adverse events.
Yang[44] 2014	3 RCTs and 3 Retrospective studies	To evaluate the effectiveness and safety of TACE plus sorafenib versus TACE alone for unresectable HCC.	OS, TTP, objective response and adverse events
Cai R[45] 2017	9 RCTs and 5 non-RCTs	To assess the efficacy and safety of the combination treatment in patients with advanced HCC.	ORR, DCR, OS and adverse events.

Abbreviations: OS, overall survival; ORR, overall response rate; DCR, disease control rate; DPR, disease progression rate; AFP, alpha-fetoprotein; TTP, time of disease progression; PFR, progression free rate; VEGF, vascular endothelial growth factor; TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma; RCT, randomized controlled trials.

Main Outcomes

Overall Survival

Ten meta-analyses[34,35,37–42,44,45] reported data on OS, and seven (7/10, 70%) found a significant improvement in OS in the TACE plus sorafenib group compared to TACE alone, with low-level certainty of evidence according to the GRADE (Supplementary Table S1).

Table 3 The Results of the Methodological Quality Assessment of the Meta-Analysis

Study	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Quality Assessments
Cheng Z[37]	2020	Y	Y	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Li D[34]	2021	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Zeng J[38]	2016	Y	PY	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Zhang L[39]	2014	N	PY	N	PY	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	Critically low
Li L[40]	2018	N	PY	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	Critically low
Hu M[35]	2016	Y	PY	N	PY	Y	N	N	Y	N	N	Y	N	Y	Y	Y	Y	Critically low
Jin PP[42]	2018	Y	Y	Y	PY	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Fu Q[43]	2014	N	Y	N	Y	Y	N	N	Y	Y	N	N	Y	N	Y	Y	Y	Critically low
Yang M[44]	2014	Y	PY	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Cai R[45]	2017	Y	PY	Y	PY	N	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	Low
Zhang X[41]	2017	Y	PY	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Xie Y[36]	2021	Y	Y	Y	PY	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low

Survival Rate

Three meta-analyses[37,41,45] reported data on 0.5-year, 1-year, and 2-year survival rates, and all these meta-analyses found significant improvements in the TACE plus sorafenib group compared to TACE alone, with low to very low level certainty of evidence according to the GRADE (Supplementary Table S1).

Time of Disease Progression

TTP was mentioned in nine meta-analyses,[34,35,37–42,44] and seven (7/9, 77.8%) found a significant improvement in TTP in the TACE plus sorafenib group compared to TACE alone, with a moderate level certainty of evidence according to the GRADE (Supplementary Table S1).

Overall Response Rate

Ten[34,36–39,41–45] included meta-analyses reporting data on ORR, and seven (7/10, 70%) included meta-analyses found a significant improvement in ORR in the TACE plus sorafenib group compared to TACE alone, with a moderate level of certainty of evidence according to the GRADE (Supplementary Table S1).

Disease Control Rate

Seven meta-analyses[34,36,38,40–42,45] reported data on DCR, and four (4/7, 57.14%) found a significant improvement in ORR in the TACE plus sorafenib group compared to TACE alone, with moderate certainty of evidence according to the GRADE (Supplementary Table S1).

Adverse Events

All Grade Adverse Event

Five meta-analyses[34,38,42,44,45] reported data on fatigue, and four (4/5, 80%) found that the incidence of fatigue was higher in the TACE plus sorafenib group than in the TACE alone group, with a moderate level of certainty of evidence according to the GRADE (Supplementary Table S2).

Two studies[34,44] included meta-analyses reporting data on nausea, and one (1/2, 50%) meta-analysis found that the incidence of nausea was higher in the TACE plus sorafenib group than in the TACE alone group, with a low level certainty of evidence according to the GRADE (Supplementary Table S2).

Three[34,42,44] included meta-analyses reporting data on alopecia, and two (2/3, 50%) included meta-analyses which found that the incidence of alopecia was higher in the TACE plus sorafenib group than in the TACE alone group, with a low-level certainty of evidence according to the GRADE (Supplementary Table S2).

Five meta-analyses[34,38,42,44,45] reported data on hand–foot skin reactions, and all included meta-analyses found that the incidence of hand–foot skin reactions was higher in the TACE plus sorafenib group than in the TACE alone group, with low level certainty of evidence according to the GRADE (Supplementary Table S2).

Five meta-analyses[34,38,42,44,45] reported data on rashes, and all included meta-analyses showed that the incidence of rashes was higher in the TACE plus sorafenib group than in the TACE alone group, with a low level of certainty of evidence according to the GRADE (Supplementary Table S2).

Two meta-analyses[42,44] reported data on hematological events, and none of the included meta-analyses found that the incidence of hematological events was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with very low certainty of evidence according to the GRADE (Supplementary Table S2).

Five meta-analyses[34,38,42,44,45] reported data on diarrhea, and all included meta-analyses found that the incidence of diarrhea was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with low level certainty of evidence according to the GRADE (Supplementary Table S2).

Five meta-analyses[34,38,42,44,45] reported that the incidence of hypertension was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with low certainty of evidence according to the GRADE (Supplementary Table S2).

One[34] included meta-analysis reported data on fever, abdominal pain, anorexia, ALT elevation, AST elevation, leukopenia, elevated bilirubin levels, and oral mucosal inflammation. This meta-analysis found that the incidence of fever, abdominal pain, anorexia, ALT elevation, AST elevation, and leukopenia was not significant in the TACE plus sorafenib treatment group compared to TACE alone, with high-level certainty of evidence according to the GRADE (Supplementary Table S2). In addition, in the TACE plus sorafenib treatment group, the incidence of elevated bilirubin levels and oral mucosal inflammation was higher than in the TACE alone group, with a high level of certainty of evidence according to the GRADE (Supplementary Table S2).

Grade 1/2 Adverse Event

One[36] included meta-analysis reported data on fatigue, nausea, hand–foot skin reactions, diarrhea, and alopecia. This meta-analysis found that the incidence of fatigue, nausea, and alopecia was not significant in the TACE plus sorafenib group compared to the TACE alone group, with a high level of certainty of evidence according to the GRADE (Supplementary Table S2). In addition, in the TACE plus sorafenib treatment group, the incidence of hand–foot skin reactions and diarrhea were higher than that in the TACE alone group, with moderate certainty of evidence according to the GRADE (Supplementary Table S2).

Grade 3/4 Adverse Event

Three meta-analyses[36,39,44] reported data on fatigue, and two of the included meta-analyses found that the incidence of fatigue was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with a low-level certainty of evidence according to the GRADE (Supplementary Table S2).

Two[36,44] included meta-analyses reported data on nausea, and none of the included meta-analyses found that the incidence of nausea was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with a low level of certainty of evidence according to the GRADE (Supplementary Table S2).

Two meta-analyses[36,44] reported data on hematological events, and none of the included meta-analyses found that the incidence of hematological events was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with a moderate level of certainty of evidence according to the GRADE (Supplementary Table S2).

Two meta-analyses[36,44] reported data on anorexia, and none of the included meta-analyses found that the incidence of anorexia was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with very low certainty of evidence according to the GRADE (Supplementary Table S2).

Four meta-analyses[36,38,39,44] reported data on hand–foot skin reactions, and three of the included meta-analyses found that the incidence of hand–foot skin reactions was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with moderate level certainty of evidence according to the GRADE (Supplementary Table S2).

Four meta-analyses[36,38,39,44] reported data on rash, and all included meta-analyses found that the incidence of rash was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with a moderate level of certainty of evidence according to the GRADE (Supplementary Table S2).

Four meta-analyses[36,38,39,44] reported data on diarrhea, and all of the included meta-analyses found that the incidence of diarrhea was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with moderate level certainty of evidence according to the GRADE (Supplementary Table S2).

Three meta-analyses[36,39,44] reported data on hypertension, and two of the included meta-analyses found that the incidence of hypertension was higher in the TACE plus sorafenib treatment group than in the TACE alone group, with a moderate level of certainty of evidence according to the GRADE (Supplementary Table S2).

Discussion

To date, 12 systematic reviews and meta-analyses have explored the clinical outcomes of TACE combined with sorafenib in advanced HCC. However, it is too early to draw robust conclusions that TACE combined with sorafenib is an effective and safe method for patients with advanced HCC, as the methodological quality of the included meta-analyses is consistent. For example, none of the included meta-analyses stated Q7 of AMSTAR2: Did the review authors provide a list of excluded studies and justify the exclusions? In addition, the certainty of most evidence is low to very low, indicating that flaws in current evidence should be noted. Although this umbrella review was conducted, further high-quality RCTs and evidence-based studies are required to explore the safety and efficacy of TACE in combination with sorafenib for advanced HCC.

Although the certainty of evidence is low to very low, in this umbrella review, TACE in combination with sorafenib showed positive results in prolonging survival and increasing tumor responses compared to TACE alone. A possible explanation for these results is that TACE and sorafenib play different roles in the treatment of HCC. Sorafenib, a multi-kinase inhibitor that can inhibit angiogenesis by selectively targeting VEGF and PDGF receptors, has been widely used for the treatment of HCC over the years, and has shown survival benefits for advanced HCC.[11,46,47] Sorafenib provided molecular insights into the metabolic changes in the miR-494/G6pc axis, together with HIF-1A activation, regulating glycogen and lipid storage.[48] Based on a Phase III randomized double-blind placebo-controlled trial conducted in the Asia-Pacific region, sorafenib prolonged the median OS from 4.2 to 6.5 months (HR=0.68; 95% CI=0.50–0.93).[49] TACE is recommended by the European Society for Medical Oncology and the American Society for Medical Oncology.[50–52] In addition, TACE directly injects anticancer drugs into the cancer cell supply arteries with a high local drug concentration in the tumor areas. In such settings, a combination of TACE and sorafenib has been used in the treatment of advanced HCC for years, and many clinical and evidence-based studies have been published. However, the effect of combination therapy is being questioned as some studies have shown negative results. For example, a large-sample multicenter RCT recently completed in South Korea indicated that TACE combined with sorafenib did not show survival benefits compared with TACE alone.[53] In addition, clinical evidence has shown that the combination of TACE and sorafenib has many more advantages than TACE alone. To solve this problem, more than ten systematic reviews and meta-analyses have been conducted to investigate this issue, but the pooled results vary. With this umbrella review, we could directly analyze published systematic reviews and meta-analyses to provide robust conclusions. However, the differences among the included studies are understandable to a certain extent, as the different etiologies and heterogeneity of HCC may lead to various responses and clinical outcomes, which could partially explain why the effects of the included meta-analyses were inconsistent.[54]

Our umbrella review also found that the combination of TACE and sorafenib resulted in a higher incidence of adverse events such as fatigue, diarrhea, elevated bilirubin, hand and foot skin reaction, rash, and hypertension. These adverse events may lead to reduction and suspension of sorafenib therapy, which should be considered in clinical practice. However, in a meta-analysis by Chen et al,[55] the authors found no significant differences in adverse events between combination therapy and sorafenib monotherapy. In addition, some clinical trials have indicated that the safety and tolerance of TACE plus sorafenib are acceptable.[56–60] It remains unclear whether the combination of TACE and sorafenib increases the incidence of adverse events.

This is the first umbrella review to systematically investigate the safety and clinical effects of TACE combined with sorafenib in advanced HCC through published systematic reviews and meta-analyses. However, similar to any evidence-based study, this umbrella review had some limitations. First, some meta-analyses included only RCTs, while the rest included both RCTs and observational studies, such as cohort studies and prospective non-RCTs.

Non-RCTs may be biased and lead to unreliable conclusions. Thus, we should also focus on the associations identified in observational studies. Second, the credibility of the umbrella review depends directly on the meta-analyses included, which may lead to inevitable conclusions. Third, in the GRADE assessment, we found that the methodological quality of most of the included evidence was low to very low based on AMSTAR2 analyses. Fourth, the TACE protocols in different studies were different, and the baseline of the included patients was also different. Due the low evidence certainty and the low methodological quality of most of the included evidence, the conclusions need to be verified by future clinical evidence. For example, some studies used different doses and combinations of TACE-related drugs such as lipiodol, lobaplatin, epirubicin, and mitomycin C, etc.

Conclusions

In conclusion, the association between TACE and sorafenib is supported by evidence. Our umbrella review found that TACE plus sorafenib enhanced survival and tumor response. In addition, the combination of TACE and sorafenib showed a higher incidence of adverse events such as fatigue, diarrhea, elevated bilirubin, hand and foot skin reaction, rash, and hypertension. However, clinicians should interpret our results with caution when applying them in clinical practice, and high-quality studies are required to confirm our results.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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