Efficacy of treatment regimens for advanced hepatocellular carcinoma
A network meta-analysis of randomized controlled trials
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Abstract
Background: This study aimed to perform a network meta-analysis to evaluate the therapeutic effect and safety of various modalities in treating advanced hepatocellular carcinoma (HCC). Typically, the modalities of interest were comprised of sorafenib, transarterial chemoembolization (TACE), sorafenib combined with TACE, TACE combined with traditional Chinese medicine (TCM), and sorafenib combined with hepatic arterial infusion chemotherapy (HAIC).

Methods: Potentially eligible studies were systematically retrieved from the electronic databases (including PubMed and Cochrane Library) up to September 2018. The overall survival (OS) associated with the 5 modalities of interest enrolled in this study was compared by means of network meta-analysis. Meanwhile, major adverse events (AEs) were also evaluated.

Results: The current network meta-analysis enrolled 7 published randomized controlled trials (RCTs), and the pooled results indicated that the TACE-TCM regimen displayed the highest efficacy in treating advanced HCC, followed by HAIC-sorafenib. By contrast, the TACE alone and sorafenib alone regimens had the least efficacy. Relative to other regimens of interest, the TACE-TCM regimen was associated with less incidence of treatment-associated AEs.

Conclusion: The TACE-TCM regimen was associated with higher treatment responses in advanced HCC patients than those of the other regimens of interest.

Abbreviations: AE = adverse event, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, HAIC = hepatic arterial infusion chemotherapy, HCC = hepatocellular carcinoma, HR = hazard ratio, OS = overall survival, RCT = randomized controlled trial, SU CRA = surface under the cumulative ranking curve, TACE = transarterial chemoembolization, TARE = transarterial radioembolization, TCM = traditional Chinese medicine, VEGF = vascular endothelial growth factor.

Keywords: advanced HCC, network meta-analysis, RCT, survival analysis

1. Introduction
Hepatocellular carcinoma (HCC) ranks the 6th place in terms of its morbidity, which is also the 3rd-leading cause of cancer-related death in the world.[1] The at-risk patients are monitored, but many patients are diagnosed at an advanced stage of the disease.[2,3] Sorafenib, an oral multikinase inhibitor, has become the preferred treatment for advanced HCC, since it had been shown to markedly improve the overall survival (OS) compared with that of placebo in the SHARP trial.[4–6] However, dose reduction or discontinuation of sorafenib is frequently necessary due to the occurrence of adverse events (AEs).[5] Transarterial therapies are the common treatments for intermediate-stage HCC. Typically, recent studies indicate that transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and repetitive hepatic arterial infusion chemotherapy (HAIC) have achieved favorable outcomes in advanced HCC. However, many patients fail to respond to the transarterial treatment, even though the optimal technique is adopted.[5] Notably, traditional Chinese medicine (TCM) has been developed and tested in different trials, which has displayed promising benefits to HCC.[8–10] Besides, As2O3 has been approved by the State Food and Drug Administration of China to be used to treat HCC since 2004.[11] Additionally, ginsenoside Rg3 has multiple antitumor activities, which can downregulate vascular endothelial growth factor (VEGF) expression, promote apoptosis, and inhibit the proliferation and invasion abilities through several signaling pathways.[12–16] Moreover, the rational combinations of the above therapies have also been developed. Chow et al.[17] and Vilgrain et al.[2] found OS did not differ significantly between TARE and sorafenib; Hu et al.[11] concluded TACE-TCM (As2O3) prolonged OS compared with TACE alone, and same result came to TACE-TCM (ginsenoside Rg3) by Zhou et al.[18] In Meyer et al.[3] and Kudo et al.[19] studies, no improvement in OS was observed when adding sorafenib to TACE;
HAIC-sorafenib yielded favorable OS when compared sorafenib alone in Ikeda et al’s study.[20]

Therefore, it is helpful to evaluate the therapeutic effect and safety of various treatment modalities. On this account, a multiarm trial is required to compare these various agents; nonetheless, evidence at such level is lacking at present. Fortunately, network meta-analysis can help to simultaneously compare 2 or more treatments.

Cucchetti et al performed a network meta-analysis of phase III randomized controlled trials (RCTs) to compare the efficacy and safety of novel drugs instead of treatment strategies for advanced HCC.[21] Tian et al conducted network meta-analysis to compare and rank different treatment strategies for HCC. However, they included cohort and RCT studies regardless of tumor stage.[22] In this study, a systemic review and network meta-analysis was carried out based on RCTs, so as to compare the therapeutic effects of 5 different therapeutic modalities (sorafenib, TACE, TACE-TCM, and HAIC-sorafenib) in advanced HCC and to rank these interventions for clinical consideration.

2. Methods

2.1. Literature retrieval strategy

Potentially eligible studies published before September 2018 were systematically retrieved in electronic databases, including PubMed and Cochrane Library. Typically, the PubMed database was retrieved using the keywords below: (((Barcelona Clinic Liver Cancer C) OR Barcelona staging C) OR BCLC C) OR (((hepatoma) OR liver cell carcinomas) OR hepatocellular carcinoma) OR liver cancer) AND ((advanced) AND Randomized Controlled Trial)[ptyp]. Meanwhile, the Cochrane database was retrieved using the strategies below: #1 ((Barcelona Clinic Liver Cancer C):ti,ab,kw OR (BCLC C):ti,ab,kw OR (Barcelona staging C):ti,ab,kw; #2 (hepatoma):ti,ab,kw OR (liver cell carcinomas):ti,ab,kw OR (hepatocellular carcinoma):ti,ab,kw OR (liver cancer):ti,ab,kw; #3 (advanced):ti,ab,kw; #4 #2 and #3; #5 #1 or #4; #6 (randomized controlled trial):pt; #7 #5 and #6. Additionally, titles of all of the references associated with the enrolled studies were manually examined, so as to obtain other potentially eligible studies.

2.2. Study inclusion and exclusion criteria

The study inclusion criteria were as follows: studies with the design of RCTs; studies that included patients with proven advanced HCC; studies with complete data on methodology, patient characteristics, AEs, and OS; studies comparing 2 arms and above, which consisted of the modalities of interest, including sorafenib, TACE (TARE), TACE-sorafenib, TACE-TCM, and HAIC-sorafenib. TARE seemed to result in similar complications and survival rates compared with TACE, and it had been considered as a safe replacement therapy to the latter.[23] Therefore, TACE and TARE were considered as one therapy in this study. Moreover, the study exclusion criteria were as follows: letters to the editor, study protocols, conference abstracts, case reports, non-RCTs, animal studies, editorials, and posters. Besides, only English literature was enrolled in this study.

2.3. Literature screening

All titles and abstracts were evaluated by 2 reviewers independently. Besides, the full texts of relevant studies and citations that could not be judged based on the abstract were obtained. To avoid the same study appeared in different publications, the institutions of authorship, treatments, study time, and study populations were identified to prevent duplicate study, and only the latest article was retained to rule of the possibility of duplication. Any disagreements among them were settled by consensus and the opinion of 3rd reviewers.

2.4. Data extraction and quality assessment

Data, including the name of first author, publication year, population characteristics, number of patients in every treatment arm, and outcomes (including OS and AEs), were extracted and summarized in an Excel file. Afterwards, the Revman tool (version 5.3) was utilized to evaluate the quality of the enrolled studies. Specifically, each study was evaluated with the judgment system below: low risk of bias, high risk of bias, or unclear (including data insufficiency or uncertainty of bias).

2.5. Statistical analysis

In this study, a network meta-analysis was carried out, so as to directly (head-to-head) and indirectly compare the treatment outcomes among various enrolled studies on advanced HCC. Moreover, the existing treatment modalities were compared using frequentist network meta-analysis in 1 single analytical framework.[24] The Stata 14.0 (StataCorp., College Station, TX) was employed to carry out the network meta-analysis; at the same time, direct and indirect therapeutic schemes were simultaneously synthesized by the “network” command and routines, and all potential comparisons between different schemes were summarized as a league table. The surface under the cumulative ranking curve (SUCRA),[25] which uses the rank probabilities from rankograms, represents a relative ranking measure, and a larger SUCRA value had indicated better rank for a certain therapy among the various therapeutic schemes available. In this study, the inconsistency was assessed in the network meta-analysis, but the results suggested that direct comparisons were lacking, and no inconsistency could be formally detected in this model.[24,26,27] As shown in Figure 1. In addition, the common heterogeneity variance for the network (τ) was employed to assess the degree of heterogeneity in all network analyses, and the values of τ < 0.5 were considered as reasonable. Finally, the network meta-analysis was presented according to the revised PRISMA guidelines of network meta-analyses.[26] That confidence interval (CI) included 1 was considered as not significant in survival analysis.

2.6. Ethical review

Ethical approval was not necessary, because this article is a meta-analysis and it does not involve the participation of ethics committee.

3. Results

3.1. Characteristics and quality assessment of the enrolled studies

Altogether 1255 related articles were identified based on the comprehensive retrieval. After removing the duplicates, the titles and abstracts of all studies were reviewed, and the full texts of
Table 1, while a
effects of all therapeutic modalities on advanced HCC with
HCC is shown in Figure 4, and Table 2 compares the therapeutic
Pairwise meta-analysis on the different treatments for advanced
3.2. Network meta-analysis of ef
be at low to moderate risks of bias.
Figure 2, and the risk of bias among those 7 enrolled articles is
illustrated in Figure 3. In summary, all enrolled articles seemed to
be at low to moderate risks of bias.

3.2. Network meta-analysis of efficacy
Pairwise meta-analysis on the different treatments for advanced
HCC is shown in Figure 4, and Table 2 compares the therapeutic
effects of all therapeutic modalities on advanced HCC with
regard to the survival rate. As could be obviously seen in the
as-generated ranking table, TACE-TCM had the highest therapeutic
effect on advanced HCC patients. Besides, network meta-analysis
on therapeutic effect was also carried out, in which TACE
(TARE) was used as the comparator, and the results suggested that
TACE-TCM had shown marked OS benefits for patients
([hazard ratio][HR]0.5-year = 2.34; 95% CI: 1.08–5.10), [HR1-
year = 2.13; 95% CI: 1.30–3.51], [HR2-year = 3.14; 95% CI: 1.26–
7.86]); however, no significant benefit could be observed on
TACE-sorafenib ([HR0.5-year = 1.24; 95% CI: 0.64–2.40], [HR1-
year = 0.82; 95% CI: 0.58–1.18], [HR2-year = 1.12; 95% CI: 0.80–
1.57]).
In addition, differences in the OS benefits of TACE (TARE)
([HR0.5-year = 0.80; 95% CI: 0.56–1.14], [HR1-year = 0.76; 95% CI:
0.60–1.05], [HR2-year = 0.95; 95% CI: 0.63–1.44]), TACE-
sorafenib ([HR0.5-year = 0.99; 95% CI: 0.46–2.12], [HR1-year =
0.65; 95% CI: 0.41–1.03], [HR2-year = 1.06; 95% CI: 0.62–1.81])
and HAIC-sorafenib ([HR0.5-year = 1.42; 95% CI: 0.53–3.86],
[HR1-year = 1.46; 95% CI: 0.65–3.28], [HR2-year = 2.35; 95% CI:
0.46–11.93]) were not statistically significant compared with that of
sorafenib.
With regard to the 2-year survival rate, results of the current
network meta-analysis demonstrated that 3 therapies, including
TACE-sorafenib (HR = 2.81; 95% CI: 1.06–7.46), TACE
(TARE) alone (HR = 3.14; 95% CI: 1.26–7.86), and sorafenib
(HR = 2.98; 95% CI: 1.09–8.15), had remarkable effects on
reducing the survival rate compared with that of TACE-TCM.
In addition, low heterogeneity was detected for the 0.5-, 1-, and
2-year OSs (τ < 0.1), and no inconsistency could be detected.

3.3. Rank test
As could be observed, it was most probable that TACE combined
with TCM was the best treatment considering OS, which had
ranked the first in hypothetical cases, followed by HAIC-
sorafenib (Fig. 5). On the contrary, TACE (TARE) alone was
predicted as the worst treatment for 0.5- and 2-year survivals,
while TACE-sorafenib had a lower 1-year survival rate. Besides,
the SUCRA values of the 5 investigated regimens were shown as
follows: TACE-TCM0.5-year = 0.891, TACE-TCM1-year = 0.895,
TACE-TCM2-year = 0.866; HAIC-sorafenib0.5-year = 0.729; HAIC-sorafenib1-year = 0.768; HAIC-sorafenib2-year = 0.666; TACE-sorafenib0.5-year = 0.381; TACE-sorafenib1-year = 0.056; TACE-sorafenib2-year = 0.405; sorafenib0.5-year = 0.298; sorafenib1-year = 0.533; sorafenib2-year = 0.432; and TACE (TARE)0.5-year = 0.202, TACE (TARE)1-year = 0.248, TACE (TARE)2-year = 0.132. The possibilities as the optimal treatment with regard to the OS are presented in the rankogram in Figure 6.

3.4. Analysis of safety

As for analysis of safety, all included studies were described merely under the condition that the authors reported AEs in different manners. For instance, Chow et al\[17\] reported 437 AEs in TARE group and 1031 in sorafenib group; whereas Vilgrain et al\[2\] witnessed 1297 AEs in their TARE group and 2837 in sorafenib group. Additionally, Meyer et al’s study suggested that, adding sorafenib seemed not to increase the TACE-associated toxicity.\[3\] Typically, the major differences were related to the well-known sorafenib-associated toxicities, including stomatitis, diarrhea, hand-foot skin reaction, rash, and bleeding. Similarly, Kudo et al’s study\[19\] showed 100% incidence of AEs in TACE-sorafenib group and 61% in TACE alone group, respectively, and most AEs were mild to moderate as expected. Moreover, it seemed to be safe to add TCM to TACE, and the difference in the incidence of AEs was not statistically significant between the 2 groups.\[11,18\] Besides, AEs were more frequently seen in HAIC-sorafenib group than in sorafenib group.\[20\]

4. Discussion

To our knowledge, this study first carried out a network meta-analysis aiming to evaluate the therapeutic effect and safety of different treatment modalities for advanced HCC patients based on all available data from the included RCTs. Notably, the pooled results demonstrated that TACE-TCM displayed the
highest therapeutic effect on advanced HCC patients. Compared with TACE alone group, the TACE combined with TCM group was associated with a higher survival rate, which could not be observed in the TACE combined with sorafenib group. Moreover, sorafenib showed no marked difference compared with TACE (TARE) in terms of patient survival, and the addition of TACE or HAIC to sorafenib could not prolong patient survival.

Sorafenib is recommended in the BCLC guidelines to be the preferred 1st-line systemic treatment for advanced HCC patients. Specifically, sorafenib has been shown to extend the survival of advanced HCC patients; however, its high cost, frequent AEs, and unsatisfactory efficacy have greatly restricted its application.[28] Specifically, TACE is an alternative option for patients with liver-confining disease, preserved hepatic function, and favorable performance status but are not appropriate for curative therapies. However, TACE is limited by its high recurrence rate, as a result of the over-expression of angiogenic and inflammatory factors, including insulin-like growth factor 2 and VEGF, which has thereby promoted the proliferation and metastasis of the residual tumor cells.[29,30] It has been explored for the feasibility of applying sorafenib following TACE as an adjuvant treatment. TACE is shown to induce acute hypoxia, which will thereby upregulate VEGF and may facilitate revascularization. Nonetheless, TACE is recommended to be used in combination with sorafenib, so as to suppress revascularization and inhibit tumor proliferation. Noteworthily, the combination of sorafenib with TACE appears to be the optimal option for advanced HCC, but its poor tolerance and high financial burden remain the urgent problems to be solved.[51,52] Kudo et al reported that 73% sorafenib-treated patients required dose reductions and 91% required interruptions.[19] Moreover, patients in the sorafenib group discontinued TACE treatments earlier.[33] These could contribute to the lack of difference in OS when adding sorafenib to TACE. HAIC can locally increase the anticancer agent concentrations in tumor and reduce the systemic distribution of these agents; besides, it is also expected to display stronger antitumor activity while less systemic AEs. Furthermore, additional sorafenib may synergistically enhance the anticancer activity.[34] Some studies indicate that TCM plays an important role in the course of terminal stage liver cancer.[35–38] For example, Sadaf et al’s results had clearly suggested that As2O3 could markedly restrict the growth and induce the apoptosis of liver cancer cells compared with normal cells.[39] Ginsenoside Rg3 possesses multiple antitumor activities, which can down-regulate the hypoxia-induced VEGF expression, promote

Figure 3. Quality assessment of included studies: (A) overall and (B) study-level risk of bias.
apoptosis, and inhibit the proliferation and invasion abilities of human cancer cells.\textsuperscript{12,14} Thus, the combination of TCM with TACE may synergistically affect the advanced HCC.

In this study, the conventional meta-analysis was compared with this network meta-analysis. In the systematic review and meta-analysis conducted by Liu et al, the therapeutic effect of TACE was compared with that of HAIC, and the results suggested that TACE was associated with higher favorable survival and response rates than HAIC in intermediate or advanced HCC patients.\textsuperscript{40} However, TACE-sorafenib and HAIC-sorafenib had not been directly compared in previous studies, but it was suggested in this study that TACE-sorafenib appeared to be equally effective to HAIC-sorafenib. In addition, in the meta-analysis conducted by Cai et al, the therapeutic effect and safety for TACE-sorafenib were assessed in advanced HCC patients. Their results suggested that the combined group exhibited marked improvements compared with TACE alone group; besides, and the AEs rates related to combined therapy were increased compared with that of TACE treatment alone.\textsuperscript{41} However, no significant survival benefit of TACE-sorafenib over sorafenib was found in our study. Actually, Cai’s study only contained 2 RCTs in English language, and the study population in 1 study was the intermediate stage HCC. Similar to our results, Wang et al had conducted a meta-analysis and systematic review, which suggested that the combined therapy could not improve the OS.\textsuperscript{42} As respected, the combined therapy might also markedly increase the risks of incidence of AEs.\textsuperscript{43} Therefore, more RCTs are required to further examine the clinical benefits of TACE-sorafenib for advanced HCC. Moreover, Lv et al indicated in a meta-analysis that the adjuvant As2O3 therapy combined with TACE could attain superior therapeutic effects over TACE alone.\textsuperscript{44}

The data of rank test demonstrated that among all the 5 investigated therapies, TACE-TCM ranked top with regard to its efficacy in improving the 0.5-, 1-, and 2-year survival rates. Furthermore, the combination of HAIC with sorafenib took the 2nd place as for the 0.5-, 1-, and 2-year survival rates. Therefore,

![Figure 4](image-url). Interval plot: (A) 0.5-year survival rate; (B) 1-year survival rate; (C) 2-year survival rate. A: sorafenib; B: TACE (TARE); C: TACE-sorafenib; D: TACE-TCM; E: HAIC-sorafenib. HAIC=hepatic arterial infusion chemotherapy, TACE=transcatheter arterial chemoembolization, TARE=transcatheter arterial radioembolization, TCM=traditional Chinese medicine.

### Table 2
Comparisons of efficacy in terms of overall survival in advanced HCC.

| Survival Rate | Treatment 1 | Treatment 2 | Hazard Ratio (95% CI) |
|---------------|-------------|-------------|----------------------|
| 0.5-y survival | HAIC-sorafenib | 0.76 (0.20, 2.65) | 1.44 (0.41, 5.04) |
|               | TACE-TCM    | 1.68 (0.69, 5.11) | 2.34 (1.08, 5.10) |
|               | TACE-sorafenib | 1.87 (0.79, 4.42) | 0.99 (0.46, 2.12) |
| 1-y survival  | HAIC-sorafenib | 0.86 (0.30, 2.33) | 2.24 (0.88, 5.68) |
|               | TACE-TCM    | 2.59 (1.40, 4.78) | 2.13 (1.30, 3.51) |
|               | TACE-sorafenib | 1.69 (0.95, 2.99) | 0.65 (0.41, 1.03) |
| 2-y survival  | HAIC-sorafenib | 0.79 (0.12, 5.33) | 2.22 (0.40, 12.25) |
|               | TACE-TCM    | 2.81 (1.06, 7.46) | 3.14 (1.26, 7.86) |
|               | TACE-sorafenib | 1.12 (0.80, 1.57) | 1.06 (0.62, 1.81) |

OR and 95% confidence interval were presented. The numbers in bold were significant. OR>1 meant the treatment in top left was better. HAIC=hepatic arterial infusion chemotherapy, OR=odds ratio, TACE=transcatheter arterial chemoembolization, TARE=transcatheter arterial radioembolization, TCM=traditional Chinese medicine.
our results suggested that the combination therapies, especially for TACE-TCM, had the greatest efficacy in terms of the prognosis for advanced HCC patients.

However, there were some limitations in this study. Firstly, the basic characteristics of all the studies enrolled might affect the possible heterogeneity as well as the final results. Secondly, estimates in this study were merely based on indirect studies since few direct comparative studies were available, which might warrant lower confidence than estimates based on direct and indirect comparative studies. Thirdly, TACE and TARE were deemed as one kind of therapy in this study to establish a network, since no significant difference was reported between TACE and TARE.[23,45] Consequently, findings of the current network meta-analysis might not completely conform to the clinical practice to some extent.

Taken together, it is revealed in the current network meta-analysis that TACE-TCM is the best therapeutic option for advanced HCC in terms of improving the OS outcomes. Nonetheless, future multicenter and high-quality RCTs with large sample sizes are warranted to confirm the advantages of the combined therapy for HCC.

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