Trans-catheter arterial chemoembolization plus Sorafenib, an unsuccessful therapy in the treatment of hepatocellular carcinoma? A systematic review and meta-analysis
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Abstract
Background: Trans-catheter arterial chemoembolization (TACE) plus Sorafenib is recommended as one of the primary means for treating hepatocellular carcinoma (HCC). This updated meta-analysis focuses on identifying the efficacy and safety of TACE plus Sorafenib versus TACE, which remains controversial despite years of exploration.

Method: PubMed, Medline, Embase, China Journal Full-text Database, Wanfang Database, and Weipu Database were used to retrieve the studies which are about comparing the clinical efficacy and safety of TACE+Sorafenib with TACE alone. The Review Manager (Version 5. 3) software was used to perform a meta-analysis of the results of studies which met the inclusion criteria recommended by the Cochrane Collaboration.

Result: Compared with TACE for treating primary HCC, TACE combined with Sorafenib can improve the 1 year, 2 years, 3 years, and 5 years overall survival rate (OS) of patients, respectively, and also improve disease control rate (DCR) and objective response rate (ORR). In terms of adverse reactions, the treatment group can lead to more complications significantly, such as hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, and so on, most of which are relevant to Sorafenib related adverse reactions, but most patients have a good prognosis after symptomatic treatment.

Conclusion: The clinical efficacy of TACE combined with Sorafenib in treating primary hepatocellular carcinoma is better than TACE, and the safety is acceptable.

Abbreviations: CR = complete remission, DCR = disease control rate, HCC = hepatocellular carcinoma, HFSR = hand-foot reaction, ORR = objective response rate, OS = overall survival rate, PD = disease progression, PR = partial response, SD = disease stabilization, TACE = trans-catheter arterial chemoembolization, TTP = time to progress, VEGF = vascular endothelial growth factor.

Keywords: hepatocellular carcinoma, liver tumor, meta-analysis, Sorafenib, transcatheter arterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is a blood-rich tumor originating from hepatocytes, and 90% of blood supply is from the hepatic artery.\textsuperscript{[1]} In the early stage, this disease was more insidious, with a high degree of malignancy and rapid progress. Most patients with HCC had already been in the middle and late stages at the time of initial diagnosis.\textsuperscript{[2,3]} In severe cases, even metastasis had occurred. For patients with advanced HCC, they have lost the opportunity for surgery, and only 15% to 20% of patients were suitable for surgery.\textsuperscript{[4,5]}

At present, trans-arterial chemoembolization (TACE) is recognized as one of the commonly used non-surgical treatments for hepatocellular carcinoma.\textsuperscript{[5]} Using TACE for the treatment of hepatocellular carcinoma has the advantages of small trauma and high targeting, which can inhibit the progression of tumor tissue significantly, and its short-term efficacy is evident.\textsuperscript{[5]} However, in many cases, tumor cells can adapt to the highly anaerobic microenvironment due to the negative feedback effect produced by TACE and incomplete embolization. Hypoxic and ischemia caused by embolism can increase the expression of HIF-1a, which could increase the expression of vascular endothelial growth factor (VEGF) and stimulate tumor neovascularization so that eventually leads to tumor recurrence and metastasis.\textsuperscript{[6]}
Sorafenib is the first Food and Drug Administration-approved targeted therapy for systemic therapy for HCC that inhibits the activity of RAF-1 serine/threonine kinase and VEGF receptors-mediated tyrosine kinase. Previous studies have shown that Sorafenib could prolong the overall survival of HCC. It is because of the complementary effect of Sorafenib and TACE that comprehensive researches are still needed to provide more useful information and theoretical basis for the clinic.

This study conducted a meta-analysis of several studies comparing the clinical efficacy of TACE with Sorafenib+TACE in treating primary HCC, including the latest research from 2018 and 2019, to explore the better choice in treating HCC.

2. Methods

2.1. Study selection

The literature should involve: the comparison of the efficacy of TACE+Sorafenib and TACE alone; more complete information (type of trial, number of cases, treatment plan, RECIST or mRECIST criteria evaluation results: complete remission [CR], partial response [PR], disease stabilization [SD], disease progression [PD], objective response rate [CR + PR = ORR], disease control rate [CR + PR + SD = DCR]), OS, and the adverse reactions associated with Sorafenib, such as hand-foot reaction (HFSR), diarrhea, high blood pressure, rash and hair loss, etc. Various outcomes of combined treatment and TACE treatment were compared comprehensively, and thus the best treatment was finally got.

2.2. Search strategy

PubMed, Medline, Embase, China Journal Full-text Database, Wanfang Database, and Weipu Database were used to retrieve the studies on comparing the clinical efficacy and safety of TACE+Sorafenib with TACE. English search terms included: the comparison of TACE+Sorafenib and TACE in treating primary HCC, according to heterogeneity test (ORR RR = 1.82, 95% CI 7.88, P = .006; DCR RR = 1.69, 95% CI 1.32–1.69, P < .00001; DCR RR = 1.21, 95% CI 1.06–1.38, P = .006) (Fig. 2).
3.3. OS
There were respectively 6, 2, 2, and 2 studies involved 1 year, 2 years, 3 years, and 5 years OS (Fig. 3). Based on heterogeneity test (1 year OS $I^2 = 89\%$, $\chi^2 = 45.12, P < .00001$; 2 years OS $I^2 = 0\%$, $\chi^2 = 0.66, P = .42$; 3 years OS $I^2 = 45\%$, $\chi^2 = 1.82, P = .18$; 5 years OS $I^2 = 25\%$, $\chi^2 = 1.33, P = .25$), the fixed effect model was used for 2 years, 3 years, and 5 years OS, and the 1-year OS was analyzed by random effect model. The results showed that the efficacy of TACE combined with Sorafenib in treating primary HCC in 1 year, 2 years, 3 years, and 5 years OS were all slightly superior to that of TACE (1 year OS RR = 1.29, 95% CI 1.00–1.67, $P = .05$; 2 years OS RR = 1.54, 95% CI 1.27–1.88, $P < .0001$; 3 years OS RR = 1.38, 95% CI 1.07–1.78, $P = .01$; 5 years OS RR = 1.66, 95% CI 1.11–2.48, $P = .01$).

3.4. Adverse effects of TACE combined with Sorafenib versus TACE
In all 15 studies, the main adverse reactions involved were: hand-foot reaction, nausea, and vomiting, fever, fatigue, diarrhea, abnormal liver function, hypertension, myelosuppression, stomatitis, rash, and hair loss, etc. The outcomes of the meta-analysis showed that the combined group have a higher risk of hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, but other adverse reactions were not statistically significant compared with the control group. After research and analysis, none of the patients died of treatment-related adverse reactions, and after the corresponding symptomatic treatment, patients were effective for their safety and tolerance (Table 2).
| Study     | Research design | Country          | Etiology                      | Group                                | Number of cases | Age (treatment/control) | Gender (male/female) | ECOG (0/1/2/3) | BCLC (A/B/C/D) | Child-Pugh (A/B/C) |
|-----------|----------------|-----------------|-------------------------------|-------------------------------------|----------------|-------------------------|----------------------|-----------------|----------------|------------------|
| Huang 2017 | RCT            | China           | NA                            | TACE + sorafenib TACE alone         | 120            | 65.17 ± 8.41/65.22 ± 8.37 | 87/33               | NA              | NA             | NA               |
| Bi 2016    | RCT            | China           | NA                            | TACE + sorafenib TACE alone         | 114            | 68.7 ± 6.6/58.9 ± 6.5    | 68/46               | NA              | NA             | NA               |
| Lv 2019    | RCT            | China           | NA                            | TACE + sorafenib TACE alone         | 120            | 51.42 ± 9.61/50.80 ± 9.58 | 78/42               | NA              | 0/70/30/0     | 86/34/0          |
| Wang 2019  | Retrospective  | China           | NA                            | TACE + sorafenib TACE alone         | 102            | 52.9 ± 6.2/52.4 ± 7.0    | 63/39               | 7/72/23/0      | 0/73/29/0      | 71/31/0          |
| Wu 2015    | RCT            | China           | HBV: 106 Other: 9             | TACE + sorafenib TACE alone         | 115            | NA                      | 70/45               | NA              | NA             | 68/49/0          |
| Xu 2015    | Retrospective  | China           | HBV: 192 HCV: 14 No Infection: 22 | TACE + sorafenib TACE alone         | 228            | 60 ± 12/61 ± 12          | 19/4/84             | NA              | NA             | 14/97/90         |
| Zhang 2016 | Retrospective  | China           | NA                            | TACE + sorafenib TACE alone         | 120            | 53.8 ± 8.1/54.6 ± 7.6    | 105/15              | 25/88/7/0      | 0/66/54/0      | 97/23/0          |
| Bai 2013   | Retrospective  | China           | HBV (213) HCV (11) No infection (16) | TACE + sorafenib TACE alone         | 246            | 54 ± 13/52 ± 12          | 219/27              | 0/64/18/2/0    | 78/139/7/1     | 178/68/0         |
| Varghese 2017 | Retrospective | India           | HBV (39) HCV (26) Ethanol (13) Cryptogenic/non-alcoholic steatohepatitis (51) | TACE + sorafenib TACE alone         | 124            | NA                      | 112/12              | 0/59/65/0      | NA             | 63/61/0          |
| Kudo 2011  | RCT            | Japan and Korea | Alcohol (31) HBV (99) HCV (287) Other (27) | TACE + sorafenib TACE + Placebo     | 458            | NA                      | 342/116             | NA             | 378/80/0/0     | NA               |
| Lencioni 2016 | Phase II, Randomized, Double-Blind SPACE Trial | Global Cooperation | HBV(105) HCV(80) Alcohol use (57) Other (65) | TACE + sorafenib TACE + Placebo     | 307            | NA                      | 261/46             | NA             | NA             | NA               |
| Peng 2019  | Retrospective  | China           | HBV (218) HCV (13) Alcohol (10) | TACE + sorafenib TACE alone         | 260            | 55 ± 7.6/56 ± 8.3       | 217/43              | 198/62/0/0     | NA             | NA               |
| Ren 2019   | Retrospective  | China           | HBV (242) HCV (18) No infection (49) | TACE + sorafenib TACE alone         | 308            | NA                      | 257/51              | 0/18/0/128/0   | NA             | 274/34/0         |
| Zheng 2017 | Retrospective  | China           | HBV (16) other (223)          | TACE + sorafenib TACE alone         | 236            | 53.88 ± 12.25/57.35 ± 11.88 | 205/01             | 153/83/0/0     | 127/91/18/0    | 172/58/5         |
| Hu 2014    | Retrospective  | China           | HBV (207) HCV (16) no infection (23) | TACE + sorafenib TACE alone         | 246            | 61 ± 11/60 ± 11         | 209/07              | NA             | NA             | 161/85/0         |
3.5. Publication bias

The funnel plot was applied to resolve the publication bias for this meta-analysis.

Figure 4 indicates that the comparison of ORR and DCR was among the 95% confidence intervals. In addition, the scatter points were distributed symmetrically in the inverted funnel. All the evidence indicates that the probability of publication bias is low.

4. Discussion

This meta-analysis evaluates the efficacy of TACE alone or TACE + Sorafenib in treating patients with advanced HCC. Compared with TACE alone in treating primary HCC, TACE combined with Sorafenib can improve the OS of patients in 1 year, 2 years, 3 years, and 5 years respectively, and can also improve the DCR and ORR. In terms of adverse reactions, the treatment group can lead to more complications significantly, such as hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, etc., and most of them are adverse reactions associated with Sorafenib. After symptomatic treatment, most patients had a good prognosis.

Kudo et al [11] in a Phase III study of Sorafenib after TACE has shown that Sorafenib did not significantly prolong time to progress (TTP) in patients who responded to TACE, which means that this combined therapy doesn’t have potential efficacy. However, he subsequently explained that this might have been due to delays in starting Sorafenib after TACE and/or low daily Sorafenib doses (200 mg twice daily used in their study vs 400 mg twice daily in the other trials)[11] therefore, in order not to affect the accuracy and reliability of the experimental results, in subsequent clinical trials, the use of sorafenib should be as soon as possible after TACE, and the adequate dosage of the drug...
should also be guaranteed. It is also doubtful that, Meyer[23] showed the treatment of Sorafenib combined with TACE is not a successful means of therapy, without any convincing meta-analysis, but meta-analysis is considered as one of the most reliable statistical methods in evidence-based medicine. So it is necessary for us to prove whether this conclusion is reliable or not.

The information in this article is more comprehensive than similar studies by Li et al[24] and Hu et al.[25] because we had analyzed the clinical efficacy of this combination therapy from more perspectives. Not only that, we also added a lot of relevant researches from 2018 and 2019, including more large-scale studies, which makes our article more time-efficient and persuasive. More importantly, the number of patients in each study we included exceeded 100, ensuring a large sample size and effectively avoiding publication bias due to the small sample size, which is also a point that has not been achieved by similar meta-analysis previously.

This study also had some shortcomings: among these 15 documents, more than half of the studies are non-randomized
controlled trials, and this study included some low-quality articles, which may have potential publication bias; in some indicators, such as the 5-year survival rate, the number of studies involved is small, which can also induce some potential publication bias; there is a lack of longer-term survival rate indicators, which allowed us to include limited information and cannot be drawn how the 2 treatment regimens perform in the long-term, for example, 10 and 20 years of clinical outcomes.

Table 2

Comparison of complications between TACE combined with Sorafenib and patients with TACE alone.

| Adverse reactions                  | Inclusion study | Heterogeneity | RR  | 95% CI          | P       |
|------------------------------------|-----------------|---------------|-----|-----------------|---------|
| Hand-foot skin reaction            | 11              | P=.0009, I=66%| 62.23 | 22.43–172.60    | <.00001 |
| Hypertension                       | 10              | P<.0001, I=74%| 11.20 | 3.76–33.41      | <.0001  |
| Diarrhea                           | 10              | P<.00001, I=87%| 12.95 | 4.12–40.78      | <.0001  |
| Weak                               | 5               | P=.001, I=84% | 1.78  | 0.89–3.52       | .10     |
| Abnormal liver function            | 6               | P<.0001, I=81%| 1.76  | 0.89–3.50       | .11     |
| Myelosuppression                   | 2               | P=.68, I=66%  | 1.26  | 0.52–3.03       | .61     |
| Rash                               | 8               | P=.004, I=66% | 4.40  | 2.25–8.63       | <.0001  |
| Hair loss                          | 7               | P<.0001, I=90%| 10.62 | 2.31–48.93      | <.002   |
| Fever                              | 5               | P=.55, I=0%   | 1.01  | 0.91–1.13       | .80     |
| Feel sick and vomit                | 5               | P=.87, I=0%   | 1.08  | 0.93–1.25       | .30     |

TACE = trans-catheter arterial chemoembolization.
5. Conclusion

The clinical efficacy of TACE combined with Sorafenib in treating primary HCC is slightly better than that of TACE, at least in the aspects of 1 year, 2 years, 3 years, and 5 years OS, ORR, DCR, moreover, the long-term efficacy is unknown. Although combination therapy can lead to Sorafenib-related adverse reactions, patients were well tolerated, according to many articles we included. Nevertheless, more large-scale researches are needed to verify this conclusion. It also needs more large-scale research about this combination therapy versus another to verify Meyer T’s conclusion.

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Author contributions

Tao Zhang: Research design, data collection, charting, article writing, and modification.

Weisen Huang: Article evaluation, data collection, data processing.

Haorong Dong: Processing data in meta-analysis, article translation, and modification.

Yijun Chen: Co-designer of this study, assists in data processing, article writing, review and modification.

References

[1] An T, Gao W, Yan Y, et al. Chinese arterial cell carcinoma via arterial chemotherapy Clinical practice guidelines for embolization therapy. Chin J Interv Radiol 2019;7:178–84.
[2] Wang W, Hou S, Chen D, et al. The efficacy and prognosis of hepatic arterial chemoembolization combined with Sorafenib in the treatment of hepatocellular carcinoma. Chin J Hepatol 2018;26:690–3.
[3] Ikai I, Ariz S, Koijro M, et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101:796–802.
[4] Lau WY, Lai EC. Hepatocellular carcinoma: current management and recent advances. Hepatobiliary Pancreat Dis Int 2008;7:237–57.
[5] Wang W, Huang Q, Ni J, et al. Meta-analysis of clinical study of TACE combined with Sorafenib in the treatment of advanced liver cancer. J Clin Radiol 2015;34:1816–21.
[6] Yan X, Yan Z, Wei Q, et al. Systematic evaluation of the efficacy of Sorafenib in patients with primary liver cancer after surgery. Mod Oncol Med 2019;27:1585–9.
[7] Peng Z, Chen S, Xiao H, et al. Microvascular invasion as a predictor of response to treatment with Sorafenib and transarterial chemoembolization for recurrent intermediate-stage hepatocellular carcinoma. Radiology 2019;292:237–47.
[8] Lei X-F, Ke Y, Bao T-H, et al. Effect and safety of Sorafenib in patients with intermediate hepatocellular carcinoma who received transarterial chemoembolization: a retrospective comparative study. World J Clin Cases 2018;6:74–83.
[9] Wei B, Yong JW, Yan Z, et al. Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: a propensity score matching study. J Dig Dis 2013;14:181–90.
[10] Hu H, Duan Z, Long X, et al. Sorafenib combined with transarterial chemoembolization versus transarterial chemoembolization alone for advanced-stage hepatocellular carcinoma: a propensity score matching study. PLoS One 2014;9:e96620 doi:10.1371/journal.pone.0096420.
[11] Kudo M, Imanaka K, Chida N, et al. Phase III study of Sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117–27.
[12] Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: THE SPACE trial. J Hepatol 2016;64:1090–8.
[13] Ren B, Wang W, Shen J, et al. Transarterial chemoembolization (TACE) combined with Sorafenib TACE alone for unresectable hepatocellular carcinoma: a Propensity Score Matching Study. J Cancer 2019;10:1189–96.
[14] Varghese J, Kedarisetty C, Venkataraman J, et al. Combination of TACE and Sorafenib improves outcomes in bclc stages b/c of hepatocellular carcinoma: a single centre experience. Ann Hepatol 2017;16:247–54.
[15] Zheng L, Guo C-Y, Chen C-S, et al. Sorafenib improves lipiodol deposition in transarterial chemoembolization of Chinese patients with hepatocellular carcinoma: a long-term, retrospective study. Oncotarget 2017;8:97613–22.
[16] Huang C, Yu W, Wang Q, et al. Clinical effect of Sorafenib combined with TACE in the treatment of primary liver cancer and its effect on bFGF and VEGF levels. J Pract Cancer 2017;32:943–5.
[17] Bi D, Zhang X. Clinical study of hepatic artery embolization chemotherapy combined with Sorafenib in the treatment of primary liver cancer. China Contemp Med 2016;23:77–9.
[18] Lu D, Wang X, Zhu H, et al. Effects of TACE combined with Sorafenib on serum HIF-1α and OPN levels in patients with advanced hepatocellular carcinoma. Hebei Med J 2019;41:1144–7.
[19] Wang J, Li R, Xu C, et al. Therapeutic effect of Sorafenib combined with tace in the treatment of advanced primary liver cancer and its effect on serum AFP and VEGF levels. Labeled Immunoassay Clin 2019;26:641–4. 670.
[20] Wu J, Korea Y, Lu S, et al. Clinical observation of hepatic artery embolization combined with Sorafenib versus simple intervention for primary liver cancer. J Nanjing Med Univ 2015;35:1739–42.
[21] Xu Y, Gao W, Liu J, et al. Efficacy of Sorafenib combined with transcatheter arterial chemoembolization in patients with advanced hepatocellular carcinoma. Cancer Pharm 2015;5:372–8.
[22] Zhang J. Therapeutic Effect of Sorafenib Combined with Transcatheter Arterial Chemoembolization in the Treatment of Advanced Liver Cancer [D]. Zhejiang: Ningbo University; 2016.
[23] Meyer T. Sorafenib and hepatic arterial infusion chemotherapy: another failed combination. Lancet Gastroenterol Hepatol 2018;3:376–7.
[24] Li L, Zhao W, Wang M, et al. Transarterial chemoembolization plus Sorafenib for the management of unresectable hepatocellular carcinoma: a systematic review and meta-analysis. BMC Gastroenterol 2018;18:13 doi:10.1186/s12876-018-0849-0.
[25] Hu M-D, Jia L-H, Liu H-B, et al. Sorafenib in combination with transarterial chemoembolization for hepatocellular carcinoma: a meta-analysis. Eur Rev Med Pharmacol Sci 2016;20:64–74.