(1) ***Scientific quality*****: yes**

(2) Language quality: yes

(3) Special requirements for figures: yes

(4) Special requirements for tables: yes

(5) ***Special requirements for references: yes***

(6) Special requirements for article highlights**:** ***yes***

(7) ***Ethical documents*****: yes**

(8) ***Approved grant application form(s) or funding agency copy of any approval document(s)*****: yes**

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Bao-Jiang Liu and colleagues submitted an interesting series on a triple therapy consisting in the combination of TACE, sorafenib and hepatic arterial infusion chemotherapy for the treatment of intermediate/advanced HCC. Although undoubtedly of interest, several issues should be properly addressed before reconsidering for acceptance:

1) **Hepatic arterial infusion chemotherapy represents a pretty unusual treatment option in hepato-concology. Make some comments on the applicability of your findings worldwide, particularly in a Western setting.**

   Thank you for your valuable suggestions. This content has been added in the introduction. Hepatic arterial infusion chemotherapy is a safe and effective treatment for advanced HCC. Oxaliplatin and 5-fluorouracil (5-FU) infused via the hepatic artery have been proven to be safe in phase I clinical studies and pharmacokinetic analyses[1, 2]. HAIC is recommended for HCC in

Japan and China[3, 4], and in Western countries[5, 6], some studies have reported the safety and efficacy of HAIC for HCC. In China and Japan, some studies have shown that HAIC combined with sorafenib or not have a survival benefit compared with sorafenib alone for advanced HCC, especially for HCC with portal vein tumor thrombus (PVTT)[7-9].

2) **Combination of TACE + sorafenib gave conflicting results in previous trials (SPACE trial, TACTICS trial). Therefore, based on the lack of definitive data on the superiority of combo therapy, why did the authors aim to add a further combination to the treatment regimen?**

Thank you for your careful review. This content has been added in introduction. The efficacy of sorafenib combined with TACE is conflicting in some trials (SPACE, TACE-2, and TACTICS). However, the TACTICS and OPTIMIS trials found that sorafenib combined with TACE benefitted PFS (TACTICS) and OS (OPTIMIS), and the timing of sorafenib was crucial in these studies. The TACTICS trial was more well-designed for evaluating the timing of sorafenib and creating a new definition of disease progression [10-12]. Sorafenib was used before TACE-HAIC to reduced vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor (PDGF) and other factors; therefore an anticancer effect was possible. Based on this theory and clinical study, we conducted exploratory phase II study.

3) **The authors claim that they conducted a prospective phase II trial. First of all, their manuscript reflects rather a prospective series than a phase II trial, as there is not a control arm (this aspect should be adequately addressed among the limitations to the study). Second, being a prospective study, it should have been registered to TrialGov or similar databases.**

Thank you for your careful review. This limitation has been added. Please review page 13, lines 8-15. During phase II trials, investigators use a sample of patients to determine whether an experimental drug or treatment is effective and safe. It is best if there is a control group to compare the safe and efficacy in this study; we will conduct a study that includes control arm, but because this study does not have a control group it can be considered a phase II study[13]. For example, investigators published results of a phase II trial examining the efficacy of sorafenib therapy with drug-eluting bead transarterial chemoembolization[14].

Thank you for your valuable suggestions. The study has been registered in the TrialGov database. The following registration number has been added: ChiCTR2000030303. Please review page 13, lines 8-15.

4) **According to current guidelines, sorafenib should not be administered to Child Pugh B patients. This is particularly true in the case of a combined treatment. Did your the local Ethics Committee made an exception?**

Thank you for your careful review. This content has been added in Table 1. It is important to carefully evaluate patients when making treatment decisions. Most clinical trials of HCC included only patients with Child-Pugh A disease in order to avoid confounding results because of the presence of liver dysfunction. In the present study, there were 9 patients (13.6%) with Child-Pugh B disease; they were all Child-Pugh B7. In addition, in the SPACE trial and another randomized controlled trial (RCT) of sorafenib combined with TACE or sorafenib alone [15-17], there was a small proportion of patients with Child-Pugh B disease (0.6-5%); the GIDEON study found that the safety profile of sorafenib appeared to be consistent across patients with Child-Pugh A and Child-Pugh B disease[18] . However, the local Ethics Committee recommended more close clinical follow-up for patients with Child-Pugh B disease.

4) **Authors performed cTACE (conventional TACE with lipiodol) in their study and then they assessed treatment response through CT scan or MRI. Tumor resopnse after cTACE should be evaluated only by means of RMI as CT scan could overestimate the response rate due to the "masking" effect of lipiodol over eventual residual viable tissue. Try to make explicit how many patients were assessed with CT scan and with MRI, and to perform a subgroup analysis based on this parameter.**

Thank you for your careful review. This content has been added in the study design and discussion. Contrast-enhanced MRI is best for evaluating tumor response. There are some reasons patients underwent contrast-enhanced CT: First, some studies[19] used contrast-enhanced CT. Second, according to the mRECIST[20], contrast-enhanced CT can be used for TACE; third, we tried to keep the imaging examination (CT or MRI) consistent before and after treatment to increase accuracy; and fourth, two

experienced radiologists with 11 and 12 years of experience in abdominal imaging determined the tumor responses by consensus.

Forty-nine patients (74.2%) underwent MRI to evaluate the tumor response, and 17 patients (25.8%) underwent CT to evaluate the tumor response; there were no significant differences (p=0.25, p=0.38) between the OS and PFS of patients who underwent MRI and CT. This content has been added in the Study Design.

5) **Overall survival should represent the primary endpoint in all oncological studies. Given the long follow-up of the series (undoubtedly the main point of strength of the study), why did authors consider PFS as the primary outcome?**

Thank you for your valuable suggestions. As you have pointed out, OS is the gold standard for cancer prognosis studies. During phase II trials, we use a small sample of patients to explore the efficacy and safety of combination therapy. We thought that the PFS could more accurately reflect the short-term efficacy of treatment. Considering that patients might receive other treatment (regorafenib, radiotherapy, ablation and particle implantation), once they have progressed after combination therapy might result in a bias in overall survival. Therefore, we set the PFS as the primary outcome and set the OS as the secondary outcome. As you suggest, we will consider overall survival as the primary endpoint in the future studies.

6) **I am impressed with the very high tumor burden and great mean nodule size of the treated patients. Moroever, the relatively high proportion of BCLC C subjects (so with portal vein thrombosis) suggests that indication to TACE was quite questionable in most of the recruited patients. In fact, BCLC C patients with PVT (provided that extrahepatic spread is absent) or huge nodule size represent ideal indications to TARE (radioembolization) rather than TACE. Please comment this aspect in the discussion, citing some of the relevant studies in the field (PMID: 26261690; PMID: 26331807; PMID: 25085684; PMID: 12630019).**

Thank you for your valuable suggestions. This content has been added in the discussion. For intermediate-stage HCC, TACE is the current standard of treatment, and drug-eluting beads TACE (DEB-TACE) provided a longer

time to progression but did not improve survival in comparison with cTACE. For HCC with PVTT or a large nodule size, transarterial radioembolization (TARE) can prolong OS compared with sorafenib or TACE. However, patients cannot access yttrium 90 in Mainland China; thus, for patients with advanced HCC (segmental portal vein thrombosis, large nodule size and Child-Pugh A disease) who do not have access to or are intolerant to sorafenib or TARE, TACE might be an alternative treatment [21-24].

8) Sixteen patients presented extrahepatic metastases, which constitute an absolute contraindication to any loco-regional treatments. Please, comment this issue.

Thank you for your valuable suggestions. This content has been added in the discussion. HCC with extrahepatic metastases is a contraindication for locoregional treatments (TACE, ablation). Most patients with HCC and extrahepatic metastases die from the progression of intrahepatic lesions; thus, it is important to control in intrahepatic lesions. Sorafenib is the first-line drug for advanced HCC, which includes HCC with PVTT and/or extrahepatic metastases[15, 17]. Systemic treatment with sorafenib combined with the local treatment of TACE-HAIC may prolong the survival. The combination of sorafenib and TACE-HAIC can may be an effective and safe therapy for HCC with extrahepatic metastases.

9) The treatment strategy is not very clear. What the approach in the case of bilobar neoplasia? Were TACE and infusion selective?

Thank you for your careful review. This content has been added in the methods. If there were bilobar HCC tumors with a low tumor burden, conventional TACE (cTACE) was performed for both tumors, and the tip of catheter was inserted into the proper hepatic artery or common hepatic artery. If there were bilobar HCC tumors with a high tumor burden, embolization of tumor was performed in steps to reduce the risk of hepatic failure. Patients with obvious variations in tumor blood supply arteries were not recruited because it is hard to keep the tip of catheter in a suitable location.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision

In this review article, the authors tried to show a benefit of an additional hepatic arterial infusion chemotherapy (HAIC) on patients with hepatocellular carcinoma (HCC) at an intermediate or advanced stage. A phase 2 clinical trial was conducted in a single institution by enrolling 66 cases as a single arm, in which HCCs were treated by transarterial chemoembolization followed by HAIC of a FOLFOX-regimen and administration of sorafenib. The inconsistent results from the previous study, which was reported in a clinical trial employing two arms in a larger cohort, requested rational explanations and discussion for anti-tumor effects, survival benefit, and adverse events for the additional HAIC. The followings are concerns that the authors may wish to consider:

1) Specific comments

Major concerns:

1. **In this report, progression-free survival (PFS) was employed for the primary endpoint even though overall survival (OS) was calculated. OS is the gold standard to confirm the efficacy of any types of cancer treatments, while PFS is only a surrogate marker. In terms of OS, 631 days was reported in a phase 3 trial, in which patients were treated with the combination of transarterial chemoembolization (TACE) and sorafenib without HAIC, and was similar with 21.8 months of OS in this report. In contrast, the median of PFS was reported as 238 days in the phase 3 trial, in which only cases at the intermediate stage were enrolled, and was substantially shorter than 13.1 months in this report, in which the cases not only at the intermediate but also advanced stage were enrolled. Furthermore, the difference of OS between Barcelona clinic liver cancer (BCLC) stages B and C of 46.1 and 15.6 months, respectively, was substantially larger than the difference of PFS between two stages of 13.5 and 9.4 months, respectively. Taken together, it is difficult to assume that the additional FOLFOX achieved beneficial effects on patients with HCC by exerting anti-tumor action. The authors should provide rational explanations and discussion for those points with an additional figure for an actual survival curve.**

   Thank you for your careful review and valuable suggestions. In the TACE-2

study[25], as you pointed out, only cases at the intermediate stage were enrolled; however, in the present study, the OS of intermediate HCC was 40.6 months, which is longer than the 631 days in the TACE-2 study. The PFS was also longer in the present study (13.5 months) than in the TACE-2 study (238 days). Because DEB-TACE did not improve overall survival compared with cTACE in some studies, HAIC may prolong the OS and PFS of intermediate HCC. There is a larger difference in OS than in PFS, and the reasons for this may be as follows: first, increasing the malignant biological behaviors and more poor prognosis of BCLC stage C HCC. Second, if the disease progresses in BCLC stage B HCC but there is a low tumor burden, there are other therapies, such as radiotherapy (n=10), ablation (n=7) and particle implantation (n=6), regorafenib. However, few patients have the chance to receive another antitumor therapy except for best supportive care (n=30) for BCLC stage C HCC. These explanations and survival curves have been added. Please review page 13, lines 8-15.

2. **As the authors mentioned, a massive deposition of lipiodol hinders the accurate evaluation of contrast enhancement in a computed tomography. If an anti-tumour effect is evaluated as a primary endpoint, an enhanced magnetic resonance imaging must be studied for the evaluation of tumour response in these cases.**

   Thank you for your careful review. This content has been added in the study design and discussion. Contrast-enhanced MRI is best for evaluating tumor response. There are some reasons patients underwent contrast-enhanced CT: First, some studies[19] used contrast-enhanced CT. Second, according to the mRECIST[20], contrast-enhanced CT can be used for TACE; third, we tried to keep the imaging examination (CT or MRI) consistent before and after treatment to increase accuracy; and fourth, two experienced radiologists with 11 and 12 years of experience in abdominal imaging determined the tumor responses by consensus.

3. **At least one serious adverse event (SAE) was reported in 65 cases out of 157 patients (41%) in the TACE + sorafenib arm of the phase 3 trial, while grade 3 or 4 adverse events were recorded only in 22 out of 66 cases in this report. How can be the additional chemotherapy of FOLFOX did cause less SAE than that in patients receiving only TACE + sorafenib without FOLFOX?**

Thank you for your careful review. This content has been added in the discussion. First, the dosages of the drugs were reduced (oxaliplatin, 60-75 mg/m2; 5-FU, 1.0-1.5g/m2); however, the dosages of intravenous medication were 130 mg/m2 (oxaliplatin) and 2.4 gm2 (5-FU), and the toxicity was tolerable. Second, the cTACE protocol used in the present study is different from the TACE protocol used in the TACE-2 study. By preserving the blood flow of the main artery to perform HAIC, cTACE results in an incomplete embolism, and chemotherapy is then infused into the tumors. The incomplete embolism can reduce AEs.

Minor concerns:

1. **Because this is a single arm study, it is hard to evaluate the benefits. To evaluate the efficacy in comparison with that of historical records, a propensity score matching or similar strategy should be adopted to compensate involved biases.**

   Thank you for your valuable suggestions. It is true that this study is a single-arm study, and there are some inevitable biases. Propensity score matching (PSM) is a good statistical method to reduce bias. We will consider using this method in future work to conduct comparative studies to evaluate the benefits of treatments.

2. **Please discuss about other treatment options for far advanced HCC.**

   Thank you for your valuable suggestions. In this study, the prognosis of advanced HCC was significantly worse than that of intermediate HCC. There are some other drugs for advanced HCC: lenvatinib as a first-line drug was approved the in REFLECT trial[26], and the median OS is 13.6 months. Regorafenib and cabozantinib are the second-line drugs for advanced HCC and were approved in the RESORCE and CELESTIAL trials[27, 28], and the median OS is 10.2-10.6 months. Nivolumab and pembrolizumab were approved in two phase II clinical trials, and the ORR was 15-15.6%[29, 30], but OS was not assessed. Radiotherapy is a common treatment method for unresectable HCC; in a meta-analysis[31], radiotherapy plus TACE was evaluated for unresectable HCC, and the OS was longer than with TACE alone (22.7 months vs 13.5 months; P<.001, respectively).

3. **Please provide a standard deviation value for age**.

   Thank you for your suggestions. Please review page 13, lines 8-15.

4. **In the "Tumor response paragraph" of Result section, complete response rates were**

described as 13.6% of 9 cases and one of 66 cases. What are these two rates for complete response?

Thank you for your careful review. The correct description should be: including 9 (13.6%) participants with complete response (CR) and 19 (28.8%) with partial response. Please review page 13, lines 8-15.

5. **Isn't cerebral hemorrhage vascular complication?**

Thank you for your careful review. Cerebral hemorrhage vascular complication is an important complication. In the present study, there were no cerebral hemorrhage vascular complications. This content has been added. Please review page 13, lines 8-15.

6. **The reference #39 is a report for gastric cancer, but not for HCC**.

Thank you for your careful review. This reference is indeed about gastric cancer. We have changed the previous reference to a phase III clinical study about HAIC with oxaliplatin, fluorouracil, and leucovorin for advanced HCC [8]. Please review page 13, lines 8-15.

7. **Please provide a report that showed safety and efficacy of oxaliplatin for HCC in comparison with cisplatin.**

Thank you for your careful review. We regret that there are no clinical reports about the safety and efficacy of oxaliplatin for HCC compared with cisplatin. There are only pharmacokinetic analyses of oxaliplatin and cisplatin administered via the hepatic artery in a VX2 tumor model in rabbits [32]. This content has been deleted. Thank you for your careful review. Oxaliplatin is a member of a new generation of platinum-based chemotherapy drugs; compared with cisplatin, oxaliplatin has distinct pharmacokinetic, biochemical, cytotoxic, and immunologic properties [32-35].

***Science Editor*:**

(1) Editorial Office Director:

title

highlight section

figures can be edited

approved grant application form has been submitted

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