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PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 54822

Title: Sorafenib combined with embolization plus hepatic arterial infusion chemotherapy for inoperable hepatocellular carcinoma

Reviewer's code: 03699961
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2020-02-20

Reviewer chosen by: Jin-Zhou Tang

Reviewer accepted review: 2020-03-27 13:22

Reviewer performed review: 2020-04-04 00:21

Review time: 7 Days and 10 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[ ] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Title: The safety and efficacy of Sorafenib combined with transcatheter arterial chemoembolization plus hepatic arterial infusion chemotherapy for intermediate and advanced HCC Liu BJ, Gao S, Zhu X, et al. 1) General Comments 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: 2) 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

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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. 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. 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? 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. 2. Please discuss about other treatment options for far advanced HCC. 3. Please provide a standard deviation value for age. 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? 5. Isn't cerebral hemorrhage vascular complication? 6. The reference #39 is a report for gastric cancer, but not for HCC. 7. Please provide a report that showed safety and efficacy of oxaliplatin for HCC in comparison with cisplatin.

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Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 54822

Title: Sorafenib combined with embolization plus hepatic arterial infusion chemotherapy for inoperable hepatocellular carcinoma

Reviewer's code: 02353723
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Adjunct Professor, Research Associate
Reviewer's Country/Territory: Italy
Author's Country/Territory: China

Manuscript submission date: 2020-02-20
Reviewer chosen by: Jin-Zhou Tang
Reviewer accepted review: 2020-03-27 09:02
Reviewer performed review: 2020-04-09 08:55
Review time: 12 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

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. 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? 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. 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? 5) Authors performed cTACE (conventional TACE with lipiodol) in their study and then they assessed treatment response through CT scan or RMI. 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 RMI, and to perform a subgroup analysis based on this parameter. 6) Overall survival should represent the primary endpoint in all oncological studies. Given the long follow-up of

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the series (undoubtedly the main point of strength of the study), why did authors consider PFS as the primary outcome? 7) 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). 8) Sixteen patients presented extrahepatic metastases, which constitute an absolute contraindication to any loco-regional treatments. Please, comment this issue. 9) The treatment strategy is not very clear. What the approach in the case of bilobar neoplasia? Were TACE and infusion selective?