May 2nd, 2018
Wang-Long Chuang,
Editor-in-Chief,
World Journal of Hepatology

Dear Dr. Chuang

My co-authors and I are grateful for the opportunity to re-submit our manuscript titled "**Treatment strategies for advanced hepatocellular carcinoma: sorafenib versus hepatic arterial infusion chemotherapy**"

The manuscript has been carefully revised, with the recommended changes made in accordance with the reviewers' suggestions as appropriate. Our responses to their comments are attached herewith. Changes made per the reviewer comments have been shown in red in the revised version of manuscript.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and better account of this manuscript. We hope that the revised manuscript is now suitable for publication in your journal.

Thank you once again; we look forward to your decision.

Sincerely,

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Reviewer #1: The review paper by Saeki et al discusses treatment strategies for advanced hepatocellular carcinomas, namely systemic therapy with Sorafenib in contrast with targeted chemotherapy administered by hepatic arterial infusion, while proposing an alternative approach in particular cases. The paper is well-written, with a focus on clinical practice and addressing major points within the current guidelines. It may be published in its current form after a brief review of the language and style. One minor suggestion for the authors would be to include recent data on novel systemic therapies and expected guidelines changes.

A. Thank you for your advice. According to the reviewer's suggestion, we have changed the EASL clinical practice guideline which has been updated in April, 2018[1]. In addition, we added information about novel systemic agents, regorafenib and lenvatinib.

Reviewer #2: This is very interesting paper. Patients with primary hepatocellular carcinoma (HCC) often develop portal venous invasion (PVI). PVI is associated with a high probability of extensive tumor spread and an elevation of portal vein pressure, which subsequently may cause esophageal varices and liver dysfunction. Few articles on the radiation therapy have been reported for the disease. Nakagawa et al clarify the efficacy and safety of three-dimensional conformal radiotherapy (3-D CRT) for PVI from HCC (Radiation therapy for portal venous invasion by HCC, World J Gastroenterology 2005). Nakazawa et al also retrospectively studied 97 patients: 40 receiving sorafenib and 57 receiving radiotherapy. After propensity score matching (28 patients in each group), patients treated with radiotherapy had a better survival compared to patients treated with sorafenib (median overall survival, 10.9 vs. 4.8 months; $p = 0.025$). Radiotherapy was an independent factor associated with survival in multivariate analysis. (Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterol 2014;14:84.) Therefore,I ask author to comment about the radiation therapy+sorafenib, HAIC+radiation therapy.

A. As pointed out but its efficacy by the reviewer, beneficial responses and excellent outcomes after radiotherapy in HCC patients with portal vein tumor thrombosis have been reported. However, radiotherapy has become recognized as an optimal treatment for HCC I the APASL and NCCN guidelines, but is not recommended in the AASLD and EASL guidelines. In addition, this review article focuses on sorafenib versus HAIC. Although we showed a combination of HAIC with radiotherapy, it is possible to use this combination therapy in clinical practice. In contrast, a few studies about a combination of sorafenib with radiotherapy have been reported, but its efficacy remains unclear because of small populations. We consider that further investigations are required in the future. In addition, there is not a recommendation in guidelines about the combination therapy, and it is difficult to use this combination therapy in clinical practice. Therefore, we did not describe the combination of sorafenib with radiotherapy.

Reviewer #3: Manuscript # 03736902 entitled, ¨Treatment strategies for advanced hepatocellular carcinoma: sorafenib versus hepatic arterial infusion chemotherapy¨ reviews the strategies for treatment of HCC with emphasis on the ¨Sorafenib¨ a multi-tyrosine kinase and angiogenesis inhibitor as an approved first-line standard systemic agent compared to , ¨hepatic arterial infusion chemotherapy (HAIC)¨. Based on the new reports and findings, authors propose that sorafenib might be used as a first-line treatment for advanced HCC patients without macroscopic vascular invasion or Child-Pugh A, while HAIC is recommended for those with macroscopic vascular invasion or Child-Pugh A or B. Comments: Over all, the review manuscript is well-written and covers the major points in the targeted subject. The figures and tables are supportive and clear. However, what that might be lacking in the present review article is quotation of the prior and recent review articles that deal with the same subject, that is ¨alternative treatment strategies compared to ¨Sorafenib¨. Authors are expected to quote these articles and compare their concluding remarks to that of those and discuss the agreements or potential contrary conclusive remarks and clarify the reason and importance of this review compared to those. In the following some examples of such review articles are shown: - Nakano M et al, Alternative treatments in advanced hepatocellular carcinoma patients with progressive disease after sorafenib treatment: a prospective multicenter cohort study. Oncotarget. 2016 - Welker MW and Trojan J. Anti-angiogenesis in hepatocellular carcinoma treatment: current evidence and future perspectives. World J Gastroenterol. 2011 - Welker MW and Trojan J Antiangiogenic treatment in hepatocellular carcinoma: the balance of efficacy and safety. Cancer Manag Res. 2013 - Yamashita T and Kaneko S. Treatment strategies for hepatocellular carcinoma in Japan. Hepatol Res. 2013. - Yu SJ and Kim YJ. Effective treatment strategies other than sorafenib for the patients with advanced hepatocellular carcinoma invading portal vein. World J Hepatol. 2015. Manuscript might be improved by inclusion of a brief description of more recent introduced therapies such as, ¨Ocoxin¨ (Díaz-Rodríguez E et al, Oncol Lett. 2017) or other examples that might be found in the recent literatures.

A. Thank you for your comments. We cited recent review articles[2, 3] and updated the EASL clinical practice guideline.

To our knowledge, there have been no reports about treatment strategies for advanced

HCC, particularly sorafenib and HAIC from a view point of reserved liver function and macroscopic vascular invasion. As this article focused on sorafenib and HAIC, the first-line treatment was either sorafenib or HAIC. Howecer, as several molecular-target was either sorafenib or HAIC. However, as several molecular-targeted and immune-oncologic agents have been developed, our draft of a treatment strategy for advanced HCC will be updated near future.

Other revised points

1. In the "Sorafenib for advanced HCC, *Current status of sorafenib*" section, we have changed sentence suppresses signal transduction pathways that mediate tumor growth growth and angiogenesis" to "Sorafenib is an oral multi-targeted kinase inhibitor that suppresses signal transduction pathways that mediate tumor growth and angiogenesis, and it was the first drug to demonstrate a survival benefit in patients with advanced HCC".
2. In the "Sorafenib versusu HAIC" section, we have deleted the part of sentence "and lenvatinib, an oral inhibitor of multi-tyrosine kinase receptors, including VEGF receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, KIT, and RET, will become another first-line treatment for such patients in the near future". In addition, we have changed the sentence "Therefore, advanced HCC patients with Child-Pugh A are candidates for both molecular-targeted drugs in general usage" to "Therefore, advanced HCC patients with Child-Pugh A are candidates for general usage of sorefenib".
3. In table 1, we have changed "Sorafenib" to "Systemic therapy (sorafenib, lenvatinib, regorafenib, and cabozantinib" because of the updated of EASL guideline.
4. In the "REFERENCES" section, we have changed the references' numbers, because we have added a few references.

REFERENCES

1 easloffice@easloffice.eu EAftSotLEa, Liver EAftSot. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

2 Kudo M. Systemic Therapy for Hepatocellular Carcinoma: 2017 Update. *Oncology* 2017; **93 Suppl 1**: 135-146 [PMID: 29258077 DOI: 10.1159/000481244]

3 Ikeda M, Morizane C, Ueno M, Okusaka T, Ishii H, Furuse J. Chemotherapy for hepatocellular carcinoma: current status and future perspectives. *Jpn J Clin Oncol* 2018; **48**(2): 103-114 [PMID: 29253194 DOI: 10.1093/jjco/hyx180]