



Sorafenib with or without concurrent transarterial chemoembolization in hepatocellular carcinoma: a cautionary comment of STAH trial

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Submitted Jun 19, 2019. Accepted for publication Nov 15, 2019.

doi: 10.21037/tcr.2019.12.51

View this article at: <http://dx.doi.org/10.21037/tcr.2019.12.51>

Conventional transarterial chemoembolization (cTACE) and sorafenib are the standard monotherapy for patients with hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer (BCLC) stage B or C by Western official guidelines (1,2). Many large randomized controlled trials have shown these two monotherapies to extend median overall survival over the best supportive care in such patients. cTACE would induce the upregulation of angiogenic factors by ischemic liver injury. Therefore, anti-angiogenic agent therapy concurrents cTACE, such as sorafenib plus cTACE, may complementarily inhibit angiogenic factors and tumor growth. Just under such a background, the STAH trial, which was published in a recent issue of *Journal of Hepatology*, was designed to assess the efficacy and safety of sorafenib concurrents cTACE in patients with advanced HCC (3).

The STAH trial included patients with stages III, IVa, or IVb HCC according to the mUICC TNM staging criteria. Advanced HCC that progressed despite prior local treatment would be included. Patients with advanced HCC progression after three cTACE sessions within the first 6 months (cTACE refractoriness) are also included. Sorafenib was started within 3 days and cTACE within 7–21 days of randomization. After median follow-up duration of 14 and 18.7 months for combination and sorafenib alone groups, they found sorafenib combined with concurrent cTACE did not improve overall survival. However, combination therapy significantly improved time to progression, progression-free survival, and tumor response rate.

We applaud Park and colleagues (3) for providing a large study so far that evaluates the efficacy of sorafenib with or

without concurrent cTACE for advanced HCC. At the same time, their conclusions should be interpreted with caution in light of some concerns which was not discussed in their study. It is reported that the efficacy of cTACE is superior to sorafenib alone. Following concerns may be the reasons of their negative findings for sorafenib concurrent cTACE.

The first concern is the type of previous therapies before involved in the present study. Of the total population, 18% were underwent hepatic resection, 21.8% underwent radiofrequency ablation or percutaneous ethanol injection, 17.1% underwent radiotherapy, and 72.3% underwent cTACE. Twenty-five percentage patients were with BCLC stage A/B HCC. Based on the addition of percentage, all patients were underwent one or more previous therapies and then had progressed or recurrent tumors. Namely, many of the included patients were with far-advanced HCCs. The main question is that more than 70% patients were being cTACE refractoriness before involved in the present study. For such patients, investigating the efficacy of addition cTACE seems pointless. It is not strange that 71% patients were with disease progression after one section of cTACE. In addition, 35% included patients were with extrahepatic spread. cTACE is useless for extrahepatic spread tumors. Therefore, the finding about similar overall survival between with and without cTACE groups seems reasonable.

The second concern is also related to the type of previous therapies before involved in the present study. Liver (re-)resection is an effective therapy for patients with recurrent tumors after liver resection or radiofrequency ablation or percutaneous ethanol injection (4,5). One fourth

of patients belonged to BCLC stage A or B in the STAHL trial. The reasons why those patients in BCLC stage A did not receive liver resection or transplantation was not explained. Importantly, any HCC treatments after stopping sorafenib therapy might affect clinical outcomes and should be reported in the trial; for example, the 2nd-line systemic therapies. On the other hand, how many patients in the BCLC stage B were down-staged and received curative treatments during the study period should also be reported. Downstaging with localized therapies, such as cTACE, could be an effective tool for identifying optimal candidates for liver resection with favorable tumor biology (6). More than 70% included patients were without vascular invasion or only with Vp1-2 vascular invasion, liver (re-)resection may be the best option for them, but not sorafenib with or without concurrent cTACE.

In conclusion, the efficacy and safety of sorafenib with or without concurrent TACE in HCC is not well illuminated.

Acknowledgments

Funding: This work was supported by the Graduate Course Construction Project of Guangxi Medical University (YJSA2017014), the National Major Special Science and Technology Project (2017ZX10203207), and ‘Guangxi BaGui Scholars’ Special Fund.

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.12.51>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358-80.
2. European Association for the Study of the Liver; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;69:182-236.
3. Park JW, Kim YJ, Kim DY, et al. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAHL trial. *J Hepatol* 2019;70:684-91.
4. Li M, Wang Z, Cao J, et al. Risk factors and prognosis of patients with recurrent hepatocellular carcinoma who undergo liver re-resections. *Eur J Surg Oncol* 2019;45:1684-90.
5. Zhang X, Li C, Wen T, et al. Outcomes of Salvage Liver Transplantation and Re-resection/Radiofrequency Ablation for Intrahepatic Recurrent Hepatocellular Carcinoma: A New Surgical Strategy Based on Recurrence Pattern. *Dig Dis Sci* 2018;63:502-14.
6. Chong JU, Choi GH, Han DH, et al. Downstaging with Localized Concurrent Chemoradiotherapy Can Identify Optimal Surgical Candidates in Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Ann Surg Oncol* 2018;25:3308-15.

Cite this article as: Chen JH, Liu X, Chen K, Hu XY, Xiang BD, Yuan WP. Sorafenib with or without concurrent transarterial chemoembolization in hepatocellular carcinoma: a cautionary comment of STAHL trial. *Transl Cancer Res* 2020;9(1):400-401. doi: 10.21037/tcr.2019.12.51