Letter to the Editor

Is FOLFOX-HAIC superior to transarterial chemoembolization in treating large hepatocellular carcinoma?

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We read with interest the recent article by Li *et al.* (1) reported a randomized phase III trial that compared the efficacy of hepatic artery infusion (HAIC) with oxaliplatin, fluorouracil, and leucovorin with transarterial chemoembolization (TACE) for large hepatocellular carcinoma (HCC) (diameter ≥7 cm). The authors found a lower incidence of serious adverse events in the FOLFOX-HAIC group; furthermore, the overall and progression-free survival was better in the FOLFOX-HAIC group than in the TACE group. Likewise, HAIC provided survival benefits in various subgroups. However, although the authors discussed some limitations, several fundamental flaws have yet to be fixed.

First, Prothrombin induced by vitamin K absence-II (PIVKA-II), as a more effective marker than alpha-fetoprotein (AFP) in detecting HCC, is a predictive marker for microvascular invasion (MVI) (2), thus related to the prognosis of HCC patients (3). HCC with an elevated level of PIVKA-II represents a more invasive subtype with early recurrence, progression and worse outcome. In the subgroup analyses of OS and PFS, only the level of AFP was included and patients were stratified according to the cut-off value of 400 ng/mL. Therefore, we suggested that the level of PIVKA-II should be included to validate the preferable efficacy of FOLFOX-HAIC further. In addition, the AFP and PIVKA-II responses are of clinical significance in monitoring treatment outcomes for HCC patients (4); in the outcome assessment of this trial, only the RECIST 1.1 criteria based on radiological characteristics was used to evaluate the tumor progression and response to treatment, for those with stable diseases (SD) assessed by RECIST 1.1 or mRECIST criteria, the changes of the AFP and PIVKA-II levels might be beneficial in further determining HCC progressions/regressions, thus need to be taken into consideration as eligible criteria.

Second, all the participating institutions were located in the south of mainland China, as it was recognized as a high-incidence area with a high mortality rate of liver cancer, owing to the prevalence of hepatitis B infection and parasitic infection caused by raw eating habits (5,6). Consequently, the accuracy of this trial may be restricted by the geographic agents.

Third, regarding inclusion criteria, the eligible patients were diagnosed with unresectable HCC in China liver cancer stage Ib-IIb; nevertheless, surgical resection rather than TACE was recommended as the most important treatment for patients staged in Ib to provide a lower recurrence rate and longer survival (7). Thus, the unresectability of the Ib HCC patients needs to be elaborated.

In summary, Li *et al.* (1) reported striking variations in survival rates between conventional TACE and the newly introduced FOLFOX-HAIC. A deeper examination of their work indicated that several critical prognostic factors for individuals with HCC were overlooked in the study

design and statistical analysis. As a result, we would like to call attention to these flaws and recommend that physicians who treat HCC participate in prospective randomized trials comparing these two approaches.

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Footnote

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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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