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Editorial OPEN ACCESS

Another treatment option for locally advanced hepatocellular carcinoma: Interventional arterial infusion of FOLFOX chemotherapy from the *FOHAIC-1* study

Ning Lyu, and Ming Zhao*

Department of Minimally Invasive and Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-Sen University Cancer Center, 651, Dongfeng East Road, Guangzhou 510060, PR China

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Abstract – Advanced stage primary hepatocellular carcinoma (HCC) accounts for more than half of all cases worldwide. Poor prognosis is mainly attributed to intrahepatic tumor burden caused by high-risk factors, including Vp4-portal vein tumor thrombosis or tumor occupancy of >50% of the liver. In 2020, the combination of a VEGF/PD-L1 blocker was superior to a single tyrosine kinase inhibitor and associated with a median overall survival of 19.2 months. However, overall survival dramatically declined from 19.2 months to 7.6 months for patients with high-risk factors. In this present study, the *FOHAIC-1* trial, interventional hepatic arterial infusion chemotherapy of FOLFOX (HAIC-FO) showed favorable survival outcomes in patients with high-risk advanced HCC. Compared with a tyrosine kinase inhibitor, in the high-risk subgroup, HAIC-FO achieved an overall survival of 10.8 months (vs. 5.7 months, hazard ratio 0.343, 95% confidence interval, 0.219–0.538). This study also observed disease downstaging in 16 (16/130) patients who received HAIC-FO; 15 (93.8%) patients received curative or regional treatments afterward. Therefore, for advanced HCC with localized high-risk factors, the clinical efficacy of HAIC-FO is significant and may be a better option than systemic therapies.

Key words: FOLFOX, Arterial Chemotherapy, Advanced Hepatocellular Carcinoma.

In primary diagnosed advanced hepatocellular carcinoma (HCC) patients, the expected median survival is concentrated within a range of 6–8 months, with a 1-year survival rate of approximately 25% [1, 2]. The IMbrave150 study has reported that atezolizumab (immune checkpoint inhibitor against programmed cell death protein-ligand 1) combined with bevacizumab (a humanized anti-vascular endothelial growth factor monoclonal antibody) has a clinically meaningful improvement in overall survival (OS) of 19.2 months versus the OS of 13.4 months in the patient cohort treated with sorafenib alone [3]. In thoroughly analyzing the baseline tumor characteristics in the IMbrave150 study, the authors found that the proportion of extrahepatic metastasis reached 63%, while Vp2–4 macrovascular invasion only accounted for 38%. This distribution is distinctly inconsistent with the epidemiology of advanced HCC in the real world [4–6]. In Asia, especially China, the area with the highest incidence of advanced HCC, newly diagnosed mega liver masses are more commonly associated with macrovascular invasion (62.8%) than extrahepatic spread [5, 6]. There is a commonsense notion in clinical practice that poor prognosis and the high mortality of advanced HCC are mainly attributed to a high burden caused by some high-risk factors in the liver, including Vp4-portal vein tumor thrombosis (PVTT) and tumor occupancy of >50% of the liver [7, 8].

We conducted a randomized controlled trial comparing interventional hepatic arterial infusion chemotherapy of FOLFOX regimens (HAIC-FO) with sorafenib in patients with advanced HCC (The FOHAIC-1 study) [9]. FOHAIC-1 mainly included patients with advanced HCC at first diagnosis (86.3%), and patients with high-risk factors (tumor involvement >50% of the liver and/or Vp4-PVTT) accounted for 49.2% of the total population (HAIC-FO group, 53.8%; sorafenib group, 44.7%). The authors found that HAIC-FO significantly improved OS (13.9 months [95% confidence interval [CI], 10.6–17.2] vs. 8.2 months [95%CI, 7.5–9.0]; hazard ratio [HR] 0.408 [95%CI, 0.301–0.552]) and progression-free survival (7.8 months [95%CI, 6.0–9.6] vs. 4.3 months [95%CI, 3.6–5.0]; HR 0.451 [95%CI, 0.340–0.598]) over sorafenib. The image findings of a case with a strong partial response are presented in Figures 1, 2, and Video 1. Moreover, a 15-gene prediction model was developed in the experimental group to identify potential beneficiaries for HAIC-FO treatment (Table 1). This prediction model identified 83% of patients who might benefit from HAIC-FO. The "HAIC-FO responder" patients also had longer progression-free survival and OS than

*Corresponding author: zhaoming@sysucc.org.cn

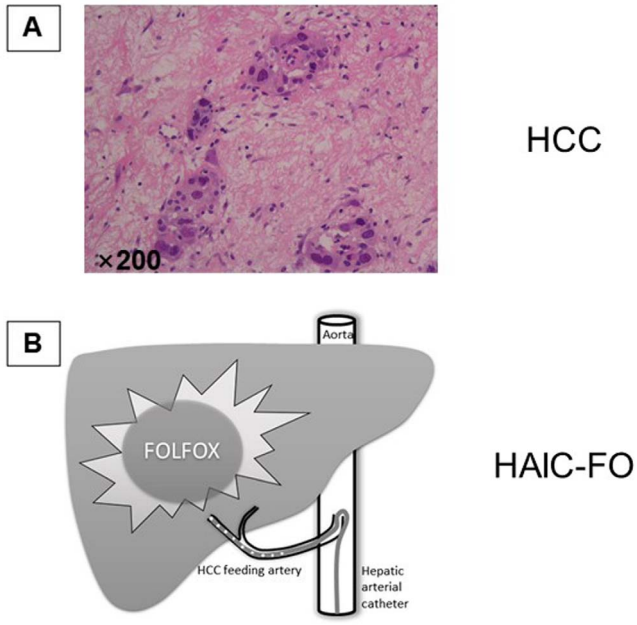


Figure 1. A 47-year-old man (tumor size on MRI scan, 22.8 cm × 10.6 cm; ECOG-PS, 2; Child-Pugh A stage) with large intrahepatic tumor diagnosed with pathologic hepatocellular carcinoma by a core need biopsy (A) and treated with first-line HAIC-FO therapy (B). HAIC-FO, interventional hepatic arterial infusion chemotherapy of FOLFOX regimens; HCC, hepatocellular carcinoma.

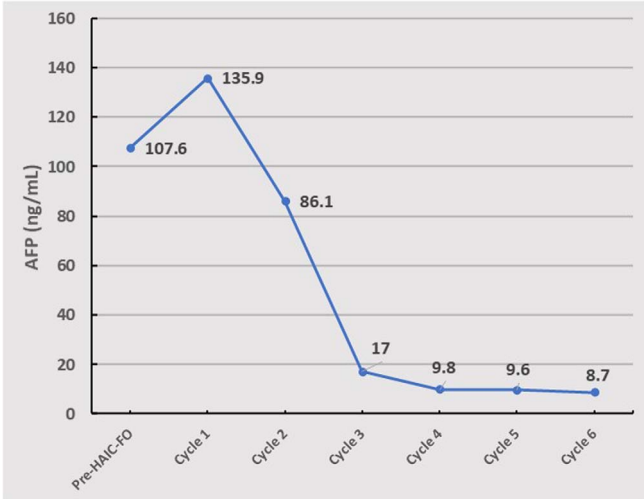
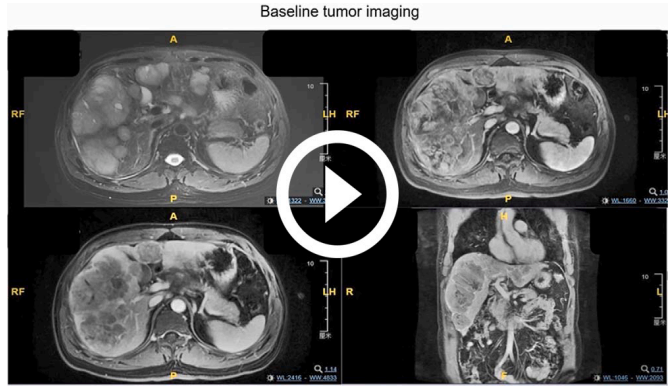


Figure 2. Dynamic change in serum AFP level of the patient mentioned in Figure 1: 107.6 ng/mL (pre-HAIC-FO treatment); 8.7 ng/mL (after 6 cycles of treatment). AFP, alpha-fetoprotein; HAIC-FO, interventional hepatic arterial infusion chemotherapy of FOLFOX regimens.

the "HAIC-FO non-responder" patients (progression-free survival: 14.3 months [95%CI, 10.4–18.2] vs. 6.2 [4.6–7.8], HR 0.363, 95%CI 0.222–0.596, P = 0.001; OS: 19.3 [15.2–23.4] vs. 10.6 [7.7–13.5], HR 0.323, 95%CI 0.186–0.560, P = 0.002).



Video 1. The video shows the dynamic response to the HAIC-FO therapy of the patient mentioned in Figure 1. After six cycles of treatment, the size of the lesions shrunk by more than 90% (strong partial response). The patient's disease was downstaged from advanced to early stage and treated with locally imaging-guided thermal ablation by the investigator's team. During a follow-up period of 49.9 months, there was no evidence of disease progression from the radiology imaging. HAIC-FO, interventional hepatic arterial infusion chemotherapy of FOLFOX regimens. https://vcm.edpsciences.org/10.1051/vcm/2022003#V1.

Table 1. Description of the 15 genes in prediction panel of HAIC-FO response.

Gene	Function
AGO2	RNA interference
ARID1B	Cell-cycle activation
AXIN2	Wnt signaling pathway
ERBB2	EGFR family
FGFR4	FGFR family
HNRNPCL4	RNA-binding
KMT2A	Transcriptional factor
NBPF20	Neuroblastoma breakpoint family
NF1	Ras signal transduction pathway
PGR	Progesterone receptor
PIK3CD	Cell growth, survival, proliferation, motility, and morphology
PRKD2	Cell proliferation
RAB3GAP2	Exocytosis of neurotransmitters and hormones regulation
SLX4	DNA repair
TCHH	Inner root sheath cells of the hair follicle regulation

The study also presented that the disease downstaging rate of patients treated with the HAIC-FO was 12.6% (16/130); 15 (93.8%) of those 16 patients received curative or loco-regional therapies afterward. Percutaneously thermal ablation (53.3% [8/15]) or transarterial chemoembolization (40% [6/15]) was preferred for HCCs downstaged to early or moderate stage, respectively. The median OS in patients who had downstaging disease treatments was significantly longer than that in those with non-downstaging (20.4 months [95%CI, 15.2–25.6] vs. 7.8 [6.5–9.1], P < 0.001). It is known that the locally arterial perfusion route can form a high concentration state of therapeutic drugs in the organ where the tumor is located, reducing the system drug concentration and potential adverse events. This method is especially suitable for tumors located regionally and dose-dependent chemotherapeutics.

Clinically, the salient feature of HAIC-FO is that it causes rapid tumor shrinkage among responding patients, promotes tumor downstaging, and creates opportunities for receiving conversion therapy, such as surgical resection or thermal ablation for HCCs.

The treatment landscape for patients with advanced HCC is changing and evolving. Considering the cohort diversity between the IMbrave 150 and the FOHAIC-1 trials, it is suggested that a head-to-head prospective study is conducted to compare the clinical benefits of HAIC-FO versus atezolizumab plus bevacizumab, especially in a population with high-risk advanced HCC patients. The development of biomolecular models to identify potential candidates for therapies with different mechanisms might also be a promising tool for optimizing the allocation of public medical resources and promoting advances in the field of precision treatment for advanced HCC.

Conflict of Interest

The authors have nothing to disclose.

References

1. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010;51(4):1274–1283. https://doi.org/10.1002/hep.23485.
2. Khalaf N, Ying J, Mittal S, et al. Natural history of untreated hepatocellular carcinoma in a US Cohort and the role of cancer surveillance. Clinical Gastroenterology and Hepatology. 2017; 15(2):273–281 e1. https://doi.org/10.1016/j.cgh.2016.07.033.
3. Finn R, Qin S, Ikeda M, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). Journal of Clinical Oncology. 2021;39(3_suppl): 267. http://doi.org/10.1200/JCO.2021.39.3_suppl.267.
4. Guarino M, Cucchetti A, Pontillo G, et al. Pattern of macrovascular invasion in hepatocellular carcinoma. European Journal of Clinical Investigation. 2021;51:e13542. https://doi.org/10.1111/eci.13542.
5. Chen ZH, Hong YF, Lin J, et al. Validation and ranking of seven staging systems of hepatocellular carcinoma. Oncology Letters. 2017;14(1):705–714. https://doi.org/10.3892/ol.2017.6222.
6. Song P, Gao J, Inagaki Y, et al. Biomarkers: evaluation of screening for and early diagnosis of hepatocellular carcinoma in Japan and china. Liver Cancer. 2013;2(1):31–39. https://doi.org/10.1159/000346220.
7. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018; 67(1):358–380. https://doi.org/10.1002/hep.29086.
8. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology. 2018;69(1):182–236. https://doi.org/10.1016/j.jhep.2018.03.019.
9. Lyu N, Wang X, Li JB, et al. Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: a biomolecular exploratory, randomized, phase III trial (FOHAIC-1). Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2022;40(5):468–480. https://doi.org/10.1200/JCO.21.01963.

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