Editorial Commentary

Effective adjuvant therapy following curative hepatectomy for hepatocellular carcinoma: a myth or reality

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Hepatocellular carcinoma (HCC) is the commonest primary liver cancer in the world, with a global incidence of around 850,000 new cases per year (1). In 2020, it is the sixth most commonly diagnosed cancer and the third cause of cancer-related death in the world (2). Most international guidelines recommend curative liver resection, radiofrequency ablation, and liver transplantation as the curative treatment options for early HCC (3). Practically, in most centres, hepatectomy is the most commonly adopted treatment for patients with HCC and compensated liver function. Nonetheless, a high incidence of intrahepatic tumor recurrence (up to 60%) limits the efficacy of hepatectomy, resulting in an unsatisfactory long-term survival of patients (4). Intrahepatic recurrence of HCC following hepatectomy can be classified as an early or late one. It is suggested that early recurrence is linked to clinically undetectable intrahepatic metastasis from the primary tumor, whereas late recurrence may originate from tumorigenesis within the underlying cirrhotic liver (5). While it is difficult to alter the underlying cirrhotic liver except by liver transplantation, there are potential adjuvant strategies to counteract the intrahepatic tumor spread to prevent early tumor recurrence, thus improving the disease's prognosis. Up till now, there are some progresses on the efficacy of adjuvant therapy for HCC after curative hepatectomy (6-8).

Adjuvant therapies following hepatectomy for HCC include antiviral therapy, transarterial chemoembolization (TACE), regional or systemic chemotherapy, molecular targeted therapy, and the latest developed immunotherapy. Of these, regional therapy, either TACE or regional infusion of chemotherapeutic drugs, has gained much attention among clinicians. Theoretically, regional therapy can eliminate tumor cells released during surgery and destroy intrahepatic pre-existing microscopic carcinomatous foci within the liver remnant to prevent future tumor recurrence. One randomized controlled trial (RCT) by Li *et al.* (9) has shown that adjuvant TACE could significantly reduce the intrahepatic recurrence rate and improved overall survival as well as disease-free survival. A recent meta-analysis of 40 studies involving 11,165 patients revealed that adjuvant TACE significantly improved overall and disease-free survival compared to surgery alone (10). Besides, the beneficial effects of adjuvant TACE can be extended to a subgroup of patients with the portal vein and hepatic vein tumor thrombus. In a large retrospective cohort of 540 patients, Liu *et al.* (11) have shown that adjuvant TACE could prolong the overall survival of patients with type II or III portal vein tumor thrombus. Similar effects of adjuvant TACE in prolonging overall and disease-free survival were also observed in patients with hepatic vein tumor thrombus (12). However, patients with hepatic vein tumor thrombus extending to the inferior vena cava may not be benefited from adjuvant TACE.

Table 1 Essential points of the study by Li *et al.* (25)

Multicenter (5 major cancer centers in China), prospective, open-label RCT
Target: 315 patients with HCC and MVI
Study period: 5 years
Interventions: 157 patients with adjuvant HAIC *vs.* 158 patients with surgery alone
Drop-out rate: 8.9% in treatment group *vs.* 9.4% in control group
Survival outcomes by intention-to-treat analysis
Median disease-free survival was better in treatment group than control (20.3 *vs.* 10 months)
Overall tumor recurrence rate was lower in treatment group than control (40.1% *vs.* 55.7%)
Absence of treatment-related severe adverse event or mortality

RCT, randomized controlled trial; HCC, hepatocellular carcinoma; MVI, microvascular invasion; HAIC, hepatic artery infusion chemotherapy.

Systemic chemotherapy has long been studied for its role as adjuvant therapy for HCC, but the results are discouraging (13). In a phase III, double-blind study (STORM trial), tyrosine kinase inhibitor (sorafenib) was administered as adjuvant therapy for up to 4 years after hepatectomy for HCC (14). There were no significant differences in the overall survival and recurrence-free survival between treatment and control groups. Consequently, adjuvant systemic chemotherapy was proven to carry no survival benefits to patients with HCC by systemic review (15). With the recent discovery of immune checkpoint inhibitors (ICIs) for various malignancies, attention has been directed to its use in HCC (16). It is believed that radiation therapy can establish synergism with immunotherapy, mainly linked to enhanced antigen presentation and reduced immunosuppressive immune infiltrate. Thus, combining an ICI with ^{90}Yttrium transarterial radioembolization might provide an encouraging effect for HCC (17). More importantly, complete remission of tumor has been reported with the use of ICIs. In a meta-analysis of the efficacy of ICIs for different malignancies, the pooled odd ratio for complete remission was 1.67 for single agent and 3.56 for double agents (18).

Along the line of chemotherapy for HCC, there were encouraging results from some studies on adjuvant hepatic artery infusion chemotherapy (HAIC) (19-22). The main advantage of adjuvant HAIC is the capability of administrating high concentrations of chemotherapeutic drugs to the liver remnant without significant systemic toxicity. Retrospective studies have shown its efficacy in prolonging the overall survival of patients with portal vein tumor thrombus (19,20). Another study has demonstrated its application in high-risk patients with multiple tumors and concomitant microvascular invasion (MVI) (21). A meta-analysis based on 11 retrospective cohort studies revealed that adjuvant HAIC resulted in better overall survival compared with surgery alone (23). However, subgroup analysis disproved its efficacy in patients with large tumors ≥7 cm. Despite these encouraging results of HAIC, the caveat is that those studies were based on retrospective cohorts only. Recently, Li *et al.* (24) reported the preliminary findings of a phase III RCT on adjuvant HAIC in patients with HCC, showing that it may be associated with survival benefits in patients with HCC having MVI. Subsequently, the present study by the same group of researchers reported the updated efficacy and safety data of adjuvant HAIC in the same cohort with an extended follow-up (25).

The essential points of the present study (25) are described in *Table 1*. It is a multicenter, prospective, open-label, RCT conducted in five major cancer centers in China. The target population was those with HCC with MVI, which was proven histologically. Through a study period of 5 years, a total of 315 patients were randomly assigned to receive adjuvant HAIC using FOLFOX (5-fluorouracil and oxaliplatin regimen) 4–6 weeks following curative hepatectomy (n=157) or surgery alone (n=158). There were 14 patients (8.9%) in the treatment group and 15 patients (9.4%) in the control group, who had dropped out due to various reasons. Eventually, the per-protocol population consisted of 143 patients in each group. By intention-to-treat analysis, the median disease-free survival rate was 20.3 months in the treatment group and 10 months in the control group. The difference was statistically significant with a hazard ratio of 0.59. The overall tumor recurrence was significantly less in the treatment group (40.1%) than in the control group (55.7%). Concerning the treatment toxicity, the majority of the adverse events were Grade 0–1 (83.8%) and there was no treatment-related death.

The merit of the present study (25) is that it is by far the first RCT demonstrating the efficacy of adjuvant HAIC using the FOLFOX regime (FOLFOX-HAIC). The multicenter study design enhances the generalization of study results in the Eastern population. Another

Table 2 Limitations of the study by Li *et al.* (25)

Relatively high incompliance rate in treatment group (15.3%)
Generalization of the study findings to Western populations is questionable
Limited data on cancer-related death

distinguishing feature is the high-risk characterization of the study population (HCC with MVI). MVI is a common histological feature of HCC and it is recognized as a major prognostic factor for tumor recurrence after curative hepatectomy (26,27). It accounts for the intrahepatic dissemination or micro-metastases from the primary tumor, leading to intrahepatic recurrence after hepatectomy. Focusing on this high-risk group helps to highlight the role of adjuvant HAIC in the prevention of intrahepatic recurrence after hepatectomy. This is by far the fundamental issue in carrying out clinical trials on adjuvant therapy for HCC. As mentioned before, HAIC allows high concentrations of the chemotherapeutic agent to be infused into the liver. Previous RCT has demonstrated the survival benefits of combined sorafenib and FOLFOX-HAIC in the treatment of locally advanced HCC with portal vein invasion. The present study has further solidified the adjuvant role of FOLFOX-HAIC. The safety issue of HAIC using the FOLFOX regime is also demonstrated in the present study. Because of the route of regional arterial infusion of FOLFOX, systemic drug toxicity has been minimized. Furthermore, the practice of performing arterial catheterization in every cycle of FOLFOX rather than using the implanted port system can avoid port-related complications, e.g., local infection, vascular thrombosis, and leakage of a chemotherapeutic drug into extrahepatic space.

Although the present study pinpointed the clinical importance of adjuvant FOLFOX-HAIC, it has certain shortcomings (*Table 2*). First, there is an issue of patient compliance with the treatment protocol. In each cycle of HAIC, patients were required to be bedridden during chemotherapy administration for 3 days, since the drug was given through a transarterial catheter. This is to avoid the dislodgement of the catheter out of the hepatic arterial system during treatment. Because of this inconvenience, 24 patients (15.3%) in the treatment group received only one cycle of HAIC. Second, this study was carried out among major cancer centres in Mainland China only, where hepatitis B infection is endemic and is the main cause of primary liver cancer. As shown in the demographic data of this study, 87.3% of recruited patients were hepatitis B carriers. Hence, whether the message of this study can be generalized to Western populations, where hepatitis C infection and metabolic syndrome are predominant etiology of HCC, is questionable. Third, although recurrence-free survival has significantly improved in the HAIC group, the overall survival was comparable in both treatment and control groups. One postulation is that the recurrent tumor in both groups can still be manageable by various treatment modalities, rendering comparable overall survival among the cohorts. There is, however, limited data regarding the rate of cancer-related death among groups in the present study.

In summary, Li *et al.* (25) reported the first multicenter RCT demonstrating the efficacy of adjuvant FOLFOX-HAIC in patients with HCC, which has MVI. The recurrence-free survival was significantly prolonged with a hazard ratio of 0.59. This study certainly adds a great impact on clinical practice, showing the solid efficacy of adjuvant FOLFOX-HAIC in high-risk patients developing postoperative intrahepatic recurrence. It also forms the basis of future clinical trials using different combinations of chemotherapeutic agents or immunotherapeutic agents. Once the practical logistics of this treatment protocol are modified to enhance patients' compliance, adjuvant FOLFOX-HAIC will no longer be a myth, but a reality.

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