Adjuvant hepatic arterial infusion chemotherapy in patients with resected hepatocellular carcinoma with microvascular invasion

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Intrahepatic recurrence can occur in up to 70% of patients at 5 years following curative-intent resection of hepatocellular carcinoma (HCC) (1,2). Although the etiology is not completely clear, intrahepatic dissemination of cancer cells during or prior to surgery and the presence of microscopic disease in the residual liver—not eliminated by surgical resection—are thought to contribute to the high incidence of recurrence (1,2). Microvascular invasion (MVI) has been well recognized as an important adverse prognostic factor even among patients who underwent a negative margins (R0) resection for HCC (3). As such, some investigators have postulated that adjuvant chemotherapy in high-risk patients might offer a survival benefit. There is no consensus, however, on the use adjuvant therapy following surgical resection of HCC. In turn, further evidence-based recommendations are needed to optimize post-resection outcomes among high-risk patients—including HCC patients with MVI.

This issue of the *Journal of Clinical Oncology* features an important study by Li and colleagues titled "Postoperative Adjuvant Hepatic Arterial Infusion Chemotherapy With FOLFOX in Hepatocellular Carcinoma With Microvascular Invasion: A Multicenter, Phase III, Randomized Study" (4). This randomized, phase III clinical trial evaluated disease-free survival (DFS) and overall survival (OS) among patients with resected (R0) HCC with MVI (n=315) who received either adjuvant hepatic arterial infusion chemotherapy (HAIC) with Folinic acid, Fluorouracil and Oxaliplatin (FOLFOX) (treatment group; n=157) or routine post-operative follow-up (control group; n=158) (4). In an intention-to-treat analysis, the median DFS in the treatment group was 20.3 months (95% CI: 10.4–30.3) versus 10.0 months in the control group (95% CI: 6.8–13.2) (P<0.001) (4). Interestingly, 1-, 2- and 3-year OS was comparable (treatment group; 93.8%, 86.4%, 80.4% *vs.* control group; 92.0%, 86.0%, 74.9%) among the two groups (P=0.13) (4). The vast majority of adverse events in the treatment group were grade 0–1 (83.8%) (4). The authors suggested that postoperative adjuvant HAIC with FOLFOX improved DFS with an acceptable toxicity rate among patients with resected HCC and MVI (4). We congratulate the authors on their efforts to address an important clinical question and provide high quality data aimed at changing clinical practice. Nevertheless, there are several points in this study that warrant discussion.

Despite a DFS benefit, treatment with HAIC FOLFOX did not translate into an OS benefit among patients with HCC and MVI. The authors suggested that the relatively short median follow-up time (23.7 months) likely did not allow for adequate assessment of the potential survival benefit related to adjuvant HAIC FOLFOX. While this reason may provide one explanation for the disparate results in DFS versus OS, it would be important to provide more details related to the causes of death in both treatment and control groups. Given that fewer patients in the treatment group experienced disease recurrence, information on cause of death in both groups may shed light on the OS data. Did patients mostly die from non-cancer, non-disease related

causes or underlying non-cancer liver disease? Alternatively, the authors should provide an analysis of disease-specific survival rather than OS, which may shed light on the disparate DFS and OS findings. Interestingly, the same group published a preliminary analysis of this phase III clinical trial in *Annals of Surgical Oncology* in 2020 (overall cohort; n=127, adjuvant arm: n=63; follow up arm: n=64) (5). Interestingly, this study reported that adjuvant HAIC FOLFOX was associated with a significant benefit in both DFS and OS among HCC patients with MVI. Of note, while not reported in the initial study, median follow-up time was likely shorter than the final analysis reported in *Journal of Clinical Oncology*. The authors should explain the discrepancy in the reported effect of HAIC FOLFOX on OS in the preliminary versus final analysis.

The "ideal" chemotherapy regimen and route of chemotherapy administration in the adjuvant setting is a topic of debate. The use of several different adjuvant therapy regimens following HCC resection have been reported with variable results (6-10). These include transcatheter arterial chemoembolization (TACE), HAIC, as well as targeted therapies based on kinase inhibitors or immune checkpoint inhibitors (ICIs) (6). In a randomized phase III trial analyzing data from 250 patients who underwent either hepatectomy alone (n=125) or adjuvant TACE following hepatectomy (n=125) for solitary tumors ≥5 cm and MVI, the TACE/hepatectomy group had a significantly longer median DFS (17.45 *vs.* 9.27 months) and OS (44.29 *vs.* 22.37 months) compared with hepatectomy alone (n=125 patients) (11). Of note, adverse effects were more common among the TACE/hepatectomy group but these were generally non-severe (11). In another phase III randomized trial comparing hepatectomy plus adjuvant TACE versus hepatectomy alone for hepatitis B-related HCC that was deemed intermediate (single tumor larger than 5 cm without MVI) or high risk (a single tumor with MVI, or two or three tumors) for recurrence, adjuvant TACE was associated with longer DFS [hazard ratio (HR), 0.68; 95% confidence interval (CI): 0.49–0.93]. and better 3-year OS rate than hepatectomy alone (85.2% *vs.* 77.4%; P=0.04; HR, 0.59; 95% CI: 0.36–0.97) with no grade 3 or 4 toxicities noted after TACE (12). Although adjuvant TACE has been demonstrated to provide a benefit in some studies (7), its applicability can be limited by complications arising post-embolization including worsening liver function from liver cell damage, reduced immunity against tumor cells, as well as increased risk of hepatitis B virus reactivation (6). In addition, prior attempts to use the multikinase inhibitor sorafenib in the adjuvant setting failed to produce any meaningful results. Indeed, the randomized controlled trial STORM demonstrated no difference in DFS or OS with the use of adjuvant sorafenib following resection or ablation of HCC (8). Furthermore, a number of clinical trials investigating whether ICIs can offer a benefit to HCC patients at high risk for recurrence after surgery or ablation are currently enrolling patients (e.g., CheckMate-9DX trial) and results are expected in the near future (6). Of note, the combination of atezolizumab/bevacizumab was recently reported to be superior to sorafenib in unresectable HCC (IMbrave150 trial) and is currently considered the standard of care in this patient population (9). An interim analysis of the IMbrave050 trial presented at the most recent 2023 American Association for Cancer Research (AACR) meeting demonstrated 28% reduced risk of recurrence or death with the combination of atezolizumab/bevacizumab compared with active surveillance in the adjuvant setting following resection or ablation of high risk HCC (10). These results need to be validated in the final completed analysis of the trial.

In the study by Li *et al.*, patients in the treatment arm received two cycles of adjuvant HAIC FOLFOX following resection of HCC with a time interval of 4–5 weeks between each cycle (4). The majority of adverse events following HAIC were grade 0–1 (83.8%) with no reported deaths related to HAIC (4). The proportion of individuals who did not complete the second cycle was relatively high (~10%); these data suggested that adjuvant HAIC likely had an impact on the quality of life. Of note, the authors compared HAIC FOLFOX versus routine follow-up and not an alternative adjuvant treatment modality. A prior randomized controlled trial by Li *et al.* demonstrated that HAIC with FOLFOX was superior to TACE relative to OS, DFS and objective response rate among individuals with large, unresectable HCC (13). The authors did not choose, however, to investigate whether adjuvant HAIC FOLFOX is superior to TACE in the adjuvant setting following resection of HCC with MVI. In addition, the optimal dose, number of chemotherapy cycles, as well as the time interval between each cycle are important parameters that warrant further investigation. In the future, comparison of adjuvant HAIC chemotherapy with other treatment modalities such as atezolizumab/bevacizumab would be valuable to discern which treatment modality can provide the most benefit in the adjuvant setting.

Investigators have recently demonstrated that apart from the presence of MVI *per se*, grading of MVI can provide

additional prognostic information. Recently, the three-tiered MVI grading system (MVI-TTG) has been proposed to classify HCC specimens as M0 (no MVI), M1 (1–5 sites of MVI and located at ≤1 cm away from the tumor-adjacent liver tissue), and M2 (>5 MVI sites or at >1 cm away from the tumor-adjacent liver tissue) (14). The presence of M2 MVI portends a higher risk of intra-hepatic recurrence even after radical resection of the disease (15). In turn, the presence of M2 MVI may necessitate a more comprehensive treatment plan including more frequent use of adjuvant therapies given the higher risk of recurrence. Unfortunately, Li *et al.* failed to stratify patients according to the MVI grading (4).

In conclusion, the use of adjuvant therapy in HCC remains an ongoing debate. Preliminary data support the use of adjuvant chemotherapy either in the form of HAIC FOLFOX or the use of combination atezolizumab/bevacizumab following resection of high-risk HCC. Further high-quality studies are needed to identify which patients may benefit the most from adjuvant therapy, as well as which adjuvant regimen may be best to prevent HCC recurrence among patients with resected high-risk HCC.

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Footnote

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