Commentary

How we use hepatic arterial infusion chemotherapy in the new era of systemic therapy?

Sadahisa Ogasawara^, Naoya Kanogawa, Naoya Kato

Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

Correspondence to: Sadahisa Ogasawara, MD, PhD. Department of Gastroenterology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, Japan. Email: ogasawaras@chiba-u.jp.

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The research article by Li *et al.* demonstrated the clinical benefits of hepatic arterial infusion chemotherapy (HAIC) (also known as transarterial infusion chemotherapy) with FOLFOX compared with transarterial chemoembolization (TACE) and sorafenib in advanced hepatocellular carcinoma (HCC) patients (1). HAIC was still selected as a common treatment option for advanced HCC mostly in Asian countries even when multi-kinase inhibitors were established as the standard treatment. It is believed that experts in Asia fully understand HAIC's clinical benefit for advanced HCC due to HAIC was a traditional transarterial treatment method which had evolved in Asia and performed before multi-kinase inhibitor development. The biggest reason HAIC had not become the global standard, even with the evidence of high-level efficacy, was the lack of well-designed clinical studies. This clinical issue has recently reached a major turning point as the effectiveness of HAIC is demonstrated in several randomized controlled trials and large cohort studies. These results would be more than sufficient to support HAIC's position as one of the major treatment options for advanced HCC.

An open-label randomized phase III study (FOHAIC-1) showed that HAIC with FOLFOX had a better survival benefit compared with sorafenib in previously untreated advanced HCC patients (19.3 versus 10.6 months, hazard ratio: 0.323, P=0.002) (2). The majority of patients in this study had highly advanced intrahepatic tumors including a median tumor size of 11.2 cm where 65.6% had macrovascular invasion. Surprisingly, clinical benefit was found in HAIC, which treated only tumors within the liver, even though more than 30% of patients had extrahepatic metastasis. This result illustrated the importance of controlling intrahepatic tumors in patients with highly advanced intrahepatic tumors through administration anticancer agents directly by HAIC. The two large cohort studies from Japan suggested that HAIC prolonged prognosis compared with sorafenib, especially in patients with macrovascular invasion (3,4). HAIC is likely to be an extremely effective treatment taken together with these results compared to sorafenib in advanced HCC patients with macrovascular invasion.

As with HAIC, TACE, which targets tumors in the liver transarterially, has long stood as a treatment choice for advanced HCC with highly advanced intrahepatic tumors. A randomized phase III trial lately demonstrated that HAIC with FOLOFX significantly improved overall survival (OS) compared with TACE in HCC patients with large intrahepatic tumor (without both macrovascular invasion or extrahepatic metastasis) (5). This randomized control trial's result was similar to those Li *et al.* initiated with clinical data from real world practice (1). The standard treatment has been TACE based on the meta-analysis result presented in the 2000s in unresectable HCC patients whose tumors are limited within the liver, at the so-called intermediate stage HCC (6). Intermediate stage HCC shows divers disease conditions depending on the tumor size and the number

^ ORCID: 0000-0002-6540-9064.

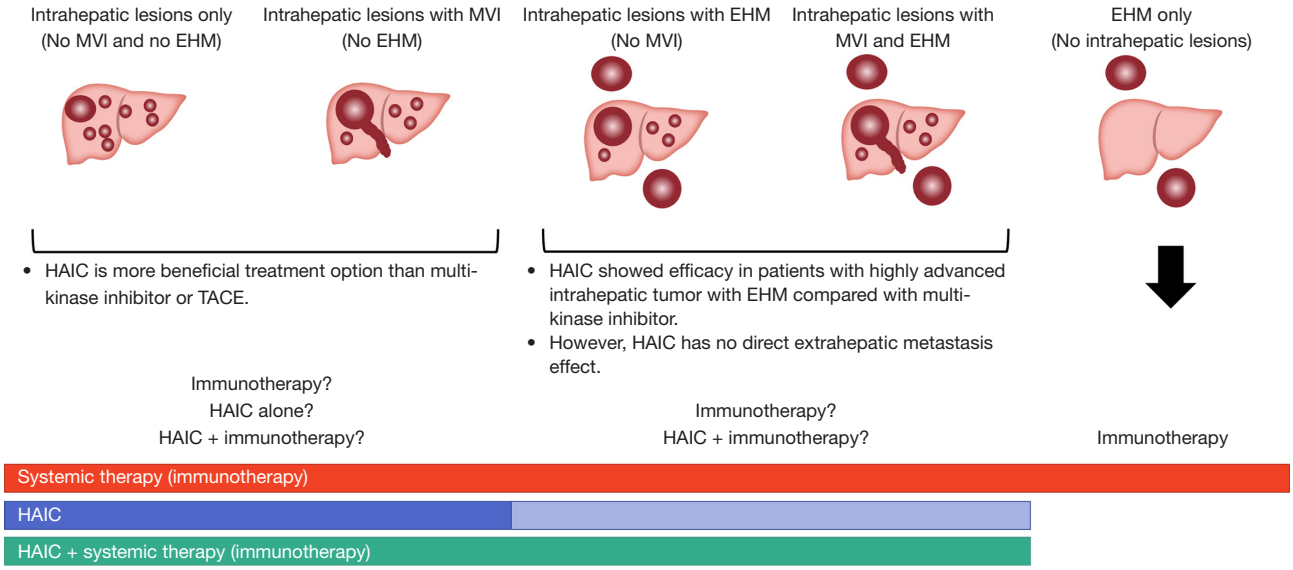

Figure 1 Advanced hepatocellular carcinoma subdivision and its optimal treatment selection; where is the best HAIC position? MVI, macrovascular invasion; EHM, extrahepatic metastasis; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization.

of intrahepatic lesions (7). It is therefore well-known that TACE treatment efficacy varied widely within intermediate stage HCC. Several recent studies have suggested that systemic therapy might be more effective than TACE in intermediate stage HCC with a high tumor burden (8). Intermediate stage HCC with high tumor burden can perhaps be dealt with as "advanced HCC (not advanced stage HCC)". In fact, this patient population has been enrolled in most systemic therapy clinical trials in patients with advanced HCC. Also, systemic therapy has been administrated in real-world practice. HAIC should be an essential treatment option in intermediate stage HCC with high tumor burden as well as systemic therapies according to the results from recent studies.

Kudo *et al.* first reported the randomized controlled trial results and compared HAIC OS combined with sorafenib and sorafenib in advanced HCC patients (9). A subgroup analysis might suggest the combination of HAIC and sorafenib's efficacy in advanced HCC with macrovascular invasion although the primary endpoint of this study was negative. Subsequently, HAIC plus sorafenib was shown to significantly prolong OS compared with sorafenib in a randomized controlled trial (RCT) from China for advanced HCC with portal vein invasion (10). The effectiveness of the combination HAIC with lenvatinib therapy and/or immune checkpoint inhibitor are gradually becoming available most recently. Results comparing HAIC plus systemic therapies including immune checkpoint inhibitor and systemic therapies alone will be available from randomized control trials being conducted in the near future.

Nowadays, immunotherapies have become a standard treatment option for advanced HCC. As immunotherapies are positioned as the mainstay of treatment, we must consider how HAIC should be used for advanced HCC patients. The heterogeneous patient's advanced HCC population should be divided into several subgroup (*Figure 1*) in discussing this clinical issue. HAIC was probably more effective than multi kinase inhibitors by controlling highly advanced intrahepatic lesions according to the results already described, even if extrahepatic metastasis were present. However, it should be understood that HAIC has no radical treatment effect on extrahepatic metastasis. We expect that combination HAIC therapies and immunotherapy will be developed that provide synergistic effects between the local HAIC control potential against intrahepatic lesions and the high probability of tumor shrinkage for both intrahepatic lesions and extrahepatic metastasis by immunological mechanisms. On the other hand, HAIC would be the most effective in advanced HCC patients with highly advanced intrahepatic lesions, with no extrahepatic metastasis. Combination therapy with HAIC and immunotherapy would be expected to be effective in this group as well. Moreover, clinical trials comparing

efficacy of HAIC and immunotherapy are also interesting. Treatment cost effectiveness will be discussed further in the near future since the medical cost of immunotherapy is very expensive. We propose to examine cost-effectiveness in addition to effectiveness of treatment in studies comparing HAIC and immunotherapy in advanced HCC patients with highly advanced intrahepatic lesions, with no extrahepatic metastasis.

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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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