Editorial

Increasing evidence for the efficacy of hepatic arterial infusion chemotherapy combined with systemic therapy for advanced hepatocellular carcinoma with macrovascular invasion: time to consider a more effective approach

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Comment on: Wu JS, Hong TC, Wu HT, *et al.* Hepatic arterial infusion chemotherapy and immune checkpoint inhibitors, alone or in combination, in advanced hepatocellular carcinoma with macrovascular invasion: a single-centre experience in Taiwan. J Gastrointest Oncol 2023;14:849-62.

Keywords: Hepatocellular carcinoma (HCC); hepatic arterial infusion chemotherapy (HAIC); molecular targeted agents; immune checkpoint inhibitor (ICI); macrovascular invasion

Submitted Sep 08, 2023. Accepted for publication Sep 22, 2023. Published online Oct 10, 2023.
doi: 10.21037/jgo-23-760
View this article at: https://dx.doi.org/10.21037/jgo-23-760

In this retrospective clinical study, Wu *et al.* demonstrated the efficacy of combination therapy for advanced hepatocellular carcinoma (HCC) with macrovascular invasion (1). Ultimately, this original article represents a timely reminder and provides a new direction on the question of which treatment options clinicians should choose for patients with advanced HCC and portal vein invasion, which is associated with a very poor prognosis.

The current treatment guidelines for HCC in Europe and the United States clearly recommend systemic chemotherapy with molecular targeting agents (MTAs) for the treatment of advanced liver cancer with vascular invasion (2). However, in reality, the treatment results are unsatisfactory (2); thus, new multidisciplinary treatment methods must be established.

The hepatic arterial infusion chemotherapy (HAIC) described in the treatment guidelines for advanced HCC in Japan and Taiwan is useful for advanced HCC with macrovascular invasion (3,4), and a novel therapy combining MTAs and HAIC may be a safe and effective treatment option that can further enhance efficacy. To demonstrate this, multicenter prospective clinical studies are needed, and this paper is considered a cornerstone study in this direction.

In 2020, primary liver cancer was the sixth most diagnosed cancer worldwide and accounted for the third most cancer-related deaths (5). Although HCC accounts for the majority of primary liver cancers in Asia and Africa, it is also steadily increasing in the West and will affect more than 1 million people annually worldwide by 2025 (6). Currently, approximately three-quarters of HCC cases are diagnosed at an unresectable advanced stage (2), and such advanced cases are generally associated with vascular invasion (7). Despite the decreasing mortality rate of liver cirrhosis, which is the main cause of HCC, the mortality rate of HCC is clearly increasing, particularly in cases classified as grade C (advanced stage) of the Barcelona Clinic Liver Cancer (BCLC) classification, with very poor 1 year survival rates of 44% (8).

Portal vein tumor thrombus (PVTT), the most frequent form of vascular invasion of HCC, is found in 10–60% of HCC cases (2). PVTT requires 8.2 and 11.5 days to infiltrate from the second branch of the portal vein to the first branch or from the first branch to the main trunk,

respectively (9), and these facts revealed the rapid growth of PVTT-HCC. Therefore, PVTT-HCC causes not only intrahepatic and extrahepatic metastases but also decreases hepatic functional reserve, which can lead to a significant narrowing of subsequent treatment options. Thus, the prognosis for patients with advanced PVTT-HCC is very poor, with a median survival period of 2.7 months in the untreated setting (2).

The latest recommendations from the European Association for the Study of the Liver and guidelines from the American Association for the Study of Liver Diseases approve the BCLC staging system for the management and prognostic prediction of HCC (2). In the staging system, any patient with PVTT-HCC is classified as having BCLC stage C (advanced stage) and a candidate for palliative systemic therapy only. Although systemic treatments are recommended for PVTT-HCC in patients with preserved liver function, they have very modest therapeutic effects (2). In reality, the basal prognosis of such patients for atezolizumab plus bevacizumab combination therapy, sorafenib monotherapy, and lenvatinib monotherapy is approximately 6 months (2). On the contrary, the consensus-based guidelines from Japan and Taiwan propose HAIC as one of the treatment options for the advanced PVTT-HCC (VP3 and VP4) (3,4). Although head-to-head comparisons among HAIC-related therapies are lacking, the clinical evidence regarding HAIC with acceptable efficacy, stability, safety, and high conversion rate in patients with PVTT-HCC is gradually increasing, particularly in Asia (3,10). In the current multidisciplinary treatment era, the use of different modalities either concomitantly or sequentially in patients with PVTT-HCC might provide a great benefit.

Drug therapy is classified into (I) chemotherapy, (II) molecular targeted therapy, and (III) immune-mediated therapy. Chemotherapy is initiated solely or in combination with surgical treatment, radiation therapy, or other drug therapies, depending on the cancer type and progression (11). By transporting cytotoxic chemical agents directly into the tumor-feeding arteries, HAIC bears higher local concentration, more substantial antitumor efficacy, and lower systemic toxicity (2). In addition, tumor cells are killed via a cytotoxic response, and normal tissue metabolism is not dependent on the hepatic vein and the resistance and metastasis induced by inflammatory factors (12).

Several antitumor chemical agents are applied for advanced HCC. Cisplatin was the first platinum drug approved as an anticancer agent in the 1970s and has been used worldwide to treat >80% of cancers (11). Because it damages not only cancer cells but also normal cells, systemic toxicity and the development of resistance limit its use. Cisplatin has various adverse effects such as digestive disorders, myelosuppression, nephrotoxicity, ototoxicity, and neurotoxicity (11). Ototoxicity frequently occurs and is irreversible, which indicates that is easily affects patients' quality of life. Compared with cisplatin, oxaliplatin has apparently improved pharmacokinetic, biochemical, and cytotoxic properties, which induce antitumor immune responses via the stimulation of proapoptotic cell calreticulin exposure (12) and has come to be widely used in clinical practice.

In the case of tumor invasion into a major vascular system or failed previous treatment, limited treatment choices are available, including systemic chemotherapy, targeted therapy, HAIC, or even best-supportive care. HAIC is considered one of the first-line treatments for advanced HCC with vascular invasion by the current guidelines of the Japan Society of Hepatology (3) and is recommended as an alternative therapy by the Chinese Society of Clinical Oncology (13), whereas the Western guidelines did not recommend HAIC as a treatment for advanced HCC because of the lack of convincing data from large-scale randomized clinical trials. Discrepancy remains among the Asia-Pacific and Western regions regarding the treatment of patients with PVTT-HCC; that is, systemic therapies are proposed as the first-line treatment for patients with PVTT-HCC in the West, whereas more radical approaches including even surgical resection have been adopted in the East (14). In the clinical practice for advanced HCC, HAIC is adopted in a case with high tumor burden or portal invasion and a case not suitable for systemic treatment (3).

HAIC was reported to be effective in reducing the incidence of intrahepatic metastasis in these patients (15) and demonstrated the non-inferior efficiency of transarterial chemoembolization (TACE) and the superior efficiency of sorafenib in patients with PVTT-HCC (2,16). In recent open-label, phase III randomized trials, oxaliplatin/fluorouracil/leucovorin (FOLFOX)-HAIC has yielded more encouraging efficacy in advanced HCC than not only TACE but sorafenib, introducing HAIC to a more worthy of recommendation status (16,17).

In the Asia-Pacific region, HAIC is widely adopted for its benefits, which include improved tumor-targeting ability, reduced effect on surrounding normal tissues, and a lower incidence of serious adverse events (12). The frequencies of grade 3–4 elevated transaminase, hyperbilirubinemia, and

the overall incidence of serious adverse events were lower in the HAIC group than in the TACE group (16). HAIC using 5-fluorouracil and cisplatin combination therapy and cisplatin monotherapy is both effective and safe for patients with advanced HCC and Child-Pugh class B (18,19).

HAIC was found to be associated with some device-related events, such as arterial obstruction, catheter blockage, subcutaneous hematoma, port displacement, or infection, and the most frequent ones were device-related (19). However, with technical improvements, these adverse events have decreased significantly, and only a few percent of patients experienced catheter-related adverse events in recent years. Considering the frequency of major adverse events observed in sorafenib-treated patients, such as systemic fatigue (43%), hand-foot skin reactions (30%), refractory diarrhea (26%), and hair loss (25%) (2), those frequencies could be acceptable in patients treated with HAIC.

As regards the poor prognosis of PVTT-HCC treated with systemic therapies, the combination of HAIC, MTAs, and/or immune checkpoint inhibitors (ICIs) is expected to exert a synergistic anticancer effect through the following reasons: (I) with a high concentration and less toxicity of anticancer drugs, HAIC can rapidly reduce the tumor burden, and MTAs exert a better antitumor effect under a lower tumor burden; (II) MTAs can help overcome resistance to chemotherapeutic agents by exerting a synergistic antitumor effect with HAIC; (III) MTAs can improve vascular permeability in HCC and augment the local drug transport by interacting with platinum transporter proteins to enhance the local enrichment of the platinum drug concentration in HCC; and (IV) chemotherapy-induced immunogenic cell death can enhance the antitumor effect of ICIs.

According to a previous report, HAIC combined with sorafenib or radiotherapy would be an alternative treatment method for patients with PVTT-HCC, indicating the superiority of HAIC in the treatment of PVTT, given its outstanding feature of stronger local control with less toxicity than systemic chemotherapy (20).

Until the mid-2010s, head-to-head comparisons among HAIC-related therapies were lacking. According to the results of network meta-analyses, HAIC-related therapy had superior outcomes in treating patients with advanced HCC including PVTT-HCC (21). Since 2020, studies have proven HAIC-based combination therapy effective in treating patients with PVTT-HCC. A high-quality HAIC phase III trial further revealed a remarkably higher objective response rate (ORR) and superior survival when combining HAIC and sorafenib for the treatment of PVTT-HCC (20). HAIC successfully increased the anticancer response of atezolizumab and bevacizumab by reducing intrahepatic tumor burden effectively and stimulating the exposure of tumor immune antigens (21). The induction therapy of FOLFOX-HAIC, PD-1 inhibitor, and MTA is an effective and safe treatment for patients with PVTT-HCC (14). A prospective phase II study of FOLFOX-HAIC, PD-1 inhibitor, and MTA demonstrated improved ORR, reaching 71% (22). The combination of intraluminal radiofrequency ablation with HAIC can be a safe potential strategy for patients with advanced biliary tract invasion (23).

Regarding physical tolerance and safety, many studies have reported the acceptable safety of combining HAIC with MTAs (14,24). Although dual immunotherapies such as durvalumab–tremelimumab and atezolizumab–bevacizumab have successfully indicated better overall survival and progression-free survival compared with sorafenib, lenvatinib remains the first-line choice for patients with PVTT in China, giving the prevalent risk of cirrhosis-related gastric bleeding (13).

In conclusion, we are now coming into the era of systemic treatments with MTAs for HCC, and combination therapy has become the mainstream for bulky and/or vascularly invading HCC. The quest for the ideal combination and the sequence set on these tumors is still unknown, and prospective clinical trials have been conducted on these matters. Multidisciplinary treatment combining locoregional therapy, including HAIC on systemic therapy such as MTAs and/or ICIs, would be a better therapeutic strategy for the management of advanced HCC. In addition, high-energy targeted radiation therapy damages tumor cells and induces their apoptosis, enhancing immune recognition, and combinations of HAIC and radiation therapy have subsequently reported better outcomes for PVTT-HCC (25). To obtain survival benefits in patients with PVTT-HCC, more attempts at seeking an ideal therapeutic combination are needed for the bright future of patients with PVTT-HCC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*.

The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-760/coif). The authors have no conflicts of interest to declare.

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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Cite this article as: Moriya K, Nagamatsu S, Uejima M, Matsuo H. Increasing evidence for the efficacy of hepatic arterial infusion chemotherapy combined with systemic therapy for advanced hepatocellular carcinoma with macrovascular invasion: time to consider a more effective approach. J Gastrointest Oncol 2023;14(5):2282-2286. doi: 10.21037/jgo-23-760

