Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-22-858

Reviewer A

Authors aimed to compare the effectiveness of hepatic arterial infusion chemotherapy and immune checkpoint inhibitors, alone or in combination, in
55 patients with advanced hepatocellular carcinoma. This is an interesting topic.
There are several concerns to be addressed.

Comment 1: The finding that ICI and HAIC, as a single modality, showed the comparable outcomes should be addressed.

Reply: We thank the reviewer for their constructive suggestion. The results comparing overall tumor responses with ICI or HAIC alone are now shown in Tables S3, and those comparing vascular responses are now shown in Table S4 and the footnote in Table 3. The results comparing OS and PFS between the ICI and HAIC groups have been shown in Figure 2 and Figure 3, respectively. In summary, no significant difference between the ICI and HAIC groups was evident in overall tumor response, vascular response, OS nor PFS. However, due to the limited patient numbers, prospective studies detailing head-to-head comparisons are needed to verify the results of the current study.

Changes in the text:
For overall tumor response, we have amended the result section and added Table S3 (please see Page 14, line 247-248, and Table S3):

"Overall ORR and DCR were also similar between the HAIC group and ICI group (Table S3)."

For vascular response, we have amended the result section and the footnote of Table 3 and added Table S4 (please see Page 15, line 252-254 and line 258-264, Table 3 and Table S4):

"ORRT was similar between the HAIC group and ICI group (P=0.572) and between the ICI group and HAIC+ICI group (P=0.064)."

"PR rate, ORRT and DCRT, and PD rate were similar between the HAIC and ICI

groups (P=0.532 for PR rate; P=0.435 for ORRT; P=0.773 for DCRT; P=0.773 for PD rate) and between the ICI group and HAIC+ICI group (P=0.077 for PR rate; P=0.031 for ORRT; P=0.020 for DCRT; P=0.020 for PD rate). There were no significant differences observed between the three groups and between the HAIC group and ICI group in IVCTT responses. (Table S4).”

For OS, we have amended the result section (please see Page 16, line 277-280):

“Although the median OS was longer in the HAIC+ICI group, there was no significant difference between the three groups (P=0.127) and any two groups (HAIC vs. ICI, P=0.987; ICI vs. HAIC+ICI, P=0.221; HAIC vs. HAIC+ICI, P=0.413) (Figure 2).”

For PFS, we have amended the result section (please see Page 16, line 285-289):

“The median PFS was numerically longer in the HAIC+ICI group than either the HAIC or the ICI monotherapy group but there was no significant difference between the three groups (P=0.091) and any two groups (HAIC vs. ICI, P=0.995; ICI vs. HAIC+ICI, P=0.225; HAIC vs. HAIC+ICI, P=0.251) (Figure 3).”

Following the suggestion of the reviewer, we have highlighted this consideration in the revised discussion resection (please see Page 23, line 409-416):

“Furthermore, the findings showed that the efficacy and incidence of severe (≥3 grade) AEs in HAIC alone and ICIs alone were comparable. In Taiwan, HAIC is covered by national health insurance, while ICIs are not. When patients cannot afford ICIs, HAIC can be an alternative. However, due to the limited patient numbers, prospective studies detailing head-to-head comparisons are needed to verify the results of the current study. Future advancements in molecular profiling techniques and a better understanding of tumor biology and biomarkers could help to identify this subset of patients. “

Comment 2: The median PFS was 9.8 months in the HAIC + ICI group. It is longer than the historical control. It should be addressed.

Reply: We sincerely appreciate the constructive comment of the reviewer. Indeed, our study showed that the combination of HAIC and ICIs had longer PFS than HAIC and ICIs alone. These results were similar to the study (J Hepatocell Carcinoma, 2021) conducted for advanced HCC treated with HAIC combined with anti-PD-1 inhibitor or

HAIC alone in which the combination therapy could provide a better PFS than HAIC alone (10.0 vs. 5.6 months, *P*=0.006). Moreover, Liu et al. (Immunotherapy, 2021) revealed that the median PFS was 10.6 months for advanced HCC patients receiving a combination of PD-1 inhibitor and HAIC therapy. These potential survival benefits might be attributed to the observation that the combination of HAIC with PD-1 inhibitors can achieve a high response rate of tumor thrombi, maintain optimal liver function, and provide opportunities for patients to receive further treatment that render long-term survival possible. However, because of the limited patient numbers in our analyses, further large cohort-based, long-term follow-up studies are required to evaluate the treatment effect of combination therapy in HCC patients.

Changes in the text: We have addressed these points in the revised discussion section following the reviewer's suggestions (please see Page 20 and 21, line 362-374):

"A real-world study in China included patients who had advanced HCC with vascular invasion or metastases receiving HAIC + PD-1 inhibitors + TKIs. The median PFS was 10.6 months. Similarly, a majority of included patients (74.1%) had PVTT (3.7% with Vp1–2, 37.0% with Vp3 and 33.3% with Vp4) (30). The median OS and PFS for HAIC+ICI treatment were similar to the previous studies in broadly similar patient populations (21,29,30). Our findings are in agreement with previous studies which HAIC combined with anti-PD-1 inhibitor could provide a survival benefit in advanced HCC patients. These observations support the clinically important implication that combination of HAIC and ICIs may contribute to the effective control of tumor thrombi, preserve liver function, and provide an opportunity for patients to receive further treatment. Further large cohort-based, long-term follow-up studies are required to evaluate the treatment effect of combination therapy in HCC patients."

Comment 3: Please, cite the related articles; PMID: 36263666/ PMID: 35443570/ PMID: 33317248

Reply: We thank the Reviewer for their suggestion. We have cited the articles, PMID: 36263666, PMID: 35443570, and PMID: 33317248.

Changes in the text: We have amended the introduction, discussion section, and the reference section (please see Page 7, line 107-110 and line 114-117, Page 23, line 414-416, Page 26, line 475-477, Page 27 line 484-486, and Page 30 and 31 line 555-557):

"Systemic therapies including tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs), vascular endothelial growth factor (VEGF) inhibitors, and a combination of an ICI and VEGF inhibitor (atezolizumab and bevacizumab) are recommended for the treatment of advanced HCC (6-9)."

"In Asia, hepatic arterial infusion chemotherapy (HAIC) has been recommended for treatment of advanced HCC with vascular invasion when systemic therapies cannot be used or have failed (12)"

"Future advancements in molecular profiling techniques and a better understanding of tumor biology and biomarkers could help to identify this subset of patients (36)."

"9. Torimura T, Iwamoto H. Optimizing the management of intermediate-stage hepatocellular carcinoma: Current trends and prospects. Clin Mol Hepatol 2021;27:236-45."

"12. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705."

"36. Lee SH, Jang HJ. Deep learning-based prediction of molecular cancer biomarkers from tissue slides: A new tool for precision oncology. Clin Mol Hepatol 2022;28:754-72."

Reviewer B

In the manuscript entitled "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", authors focus the efficacy of the combination therapy of hepatic arterial infusion chemotherapy (HAIC) and immune checkpoint inhibitors (ICI) in patients with advanced HCC. While the manuscript is well written and the findings of this study are of interest, their appeal to the readership of this journal is still limited to warrant publication. To overcome this limitation and make the article more persuasive, the authors need to demonstrate the following issues.

Comment 1: In the "Methods" section, authors defined "OS" as the length of time from

the date HAIC or ICIs was administered to death from any cause. In this retrospective study, was there any mortal case by traffic accident or suicide, for example? Authors should better treat these cases as not "death" but "censored".

Reply: We thank the reviewer for their suggestion. We have added the condition of patients censored in the method section. The patients' cause of death is summarized below. No patients died from traffic accidents, suicide or other causes of death unrelated to hepatocellular carcinoma.

	HAIC (n = 70)	**Systemic ICI** (n = 46)	**HAIC and ICI** (n = 14)
Death, n (%)	50 (71.43)	28 (60.87)	7 (50.00)
Cause of death, n (%)			
Liver failure	42 (60.00)	23 (50.00)	5 (35.71)
Septic shock	3 (4.29)	4 (8.70)	1 (7.14)
Tumor rupture with hypovolemic shock	3 (4.29)	0 (0.00)	0 (0.00)
Gastrointestinal tract bleeding	2 (2.86)	1 (2.17)	1 (7.14)

Changes in the text: We have amended the method section (please see Page 11, line 187-188 and line 190-192):

"Patients without documented death at the time of the final analysis were censored at the date of the last follow-up."

"Patients without documented disease progression or death at the time of the final analysis were censored at the date of the last follow-up."

Comment 2: Additionally, hepatic functional reserve in a patient with advanced HCC was actually important as well as his/her clinical stage of HCC. The persuasiveness of this article would be enhanced if information on changes in patients' hepatic functional reserve over time before and after treatment were presented.

Reply: We thanks for your constructive comment. We have shown the dynamic changes in the levels of serum total bilirubin before and after treatment as supplementary material, Figure S5 and Table S7. The levels of serum total bilirubin were not significantly changed in the HAIC+ICI group after 12 weeks of treatment.

Changes in the text: We have amended the result section and added Figure S5 and Table S7 (please see Page 19, line 328-333, Figure S5 and Table S7):

"Furthermore, the levels of total bilirubin tended to elevate in the ICI group (β-coefficient=0.94, P=0.010) and HAIC group (β-coefficient=0.40, P=0.001), and there was no change in the HAIC+ICI group (β-coefficient=0.23, P=0.120) after 12 weeks of treatment (Figure S5 and Table S7). It indicated that liver functional reserve in patients who received combination therapy was not significantly changed during the 12-week treatment period."

Comment 3: In this study, one-shot HAIC with doxorubicin and cisplatin in combination was administrated once a month. On the other hand, HAIC has been generally performed in the style of continuous arterial infusion with reservoir in many facilities.
From the point of this view, two of the following papers are preferably cited in the "introduction" section.
J Gastrointest Oncol. 2018 Aug;9(4):741-749
Clin Mol Hepatol. 2019 Dec;25(4):381-389

Reply: We thank the reviewer for their suggestion. We have cited these two papers in the introduction section.

Changes in the text: We have amended the introduction section and the reference section (please see Page 7 and 8, line 118-120, and Page 28, line 500-505):

"*In addition, HAIC allows repeated delivery of high concentrations of intrahepatic drugs without simultaneous embolization of the hepatic vasculature and leads to acceptable levels of toxicity (17,18)."*

"17. Moriya K, Namisaki T, Sato S, et al. Efficacy of bi-monthly hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. J Gastrointest Oncol 2018;9:741-9."

"18. Moriya K, Namisaki T, Sato S, et al. Bi-monthly hepatic arterial infusion chemotherapy as a novel strategy for advanced hepatocellular carcinoma in decompensated cirrhotic patients. Clin Mol Hepatol 2019;25:381-9."

Reviewer C

Authors retrospectively evaluated the efficacy of ICI plus HAIC for HCC with MVI as compared with ICI or HAIC alone. As authors mentioned, optimal treatment for HCC with MVI is desired. ICI plus HAIC might be expected as a treatment option for such HCC patients.

Comment 1: In present study, ICI plus HAIC was not a predictive factor in PFS. It suggested that background factors might be different in the groups, such as liver function or general conditions. Authors should consider them and compare them with matched cohort.

Reply: We sincerely appreciate the constructive comment. In the present study, HAIC+ICIs was in fact a significantly predictor of PFS, but not of OS (Tables S5 and S6). Due to the small sample size of the HAIC+ICI group, comparison of HAIC+ICI cohort with matched cohort may lack statistical power. Therefore, we have added more variables of liver function (Child–Pugh score) and general condition (ECOG) into multivariate Cox proportional hazard model for PFS. The results showed that HAIC in combination with ICIs (adjusted HR=0.48, 95% CI, 0.24–0.98, *P*=0.043) and Child–Pugh class B (adjusted HR=1.73, 95% CI, 1.10–2.74, *P*=0.019) were still independent risk factors for PFS. However, as the reviewer disclosed, the patients in our study were heterogeneous with respect to liver function reserve and performance status. In the future, more homogenous and large-scale prospective studies are needed to verify the results of the current study.

Changes in the text: We have addressed these points in the revised discussion section (please see Page 23, line 418-421):

"Second, heterogeneity may exist across three groups in terms of ECOG score, liver function reserve, distant metastases, thrombus location, prior treatment, and TKIs combination therapy. In the future, more homogenous and large-scale prospective studies are needed to verify the results of the current study."

Comment 2: Etiology of liver diseases should be clarified. If HBV was an etiology, HBV status should be also clarified (e.g. HBV-DNA, NA treatment)

Reply: We sincerely appreciate the constructive comment of the reviewer. The

etiology of liver diseases including HBV status has been added to Table 1.

Changes in the text: We have amended the result section and Table 1 (please see Page 13, line 220-223, and Table 1):

"More than half (65.4%) of patients had chronic hepatitis B, and 50% of patients were treated with nucleotide analogue therapies. 30% of patients had chronic hepatitis C. Less than 10% of patients had alcoholic hepatitis (9.2%) and nonalcoholic steatohepatitis (0.8%)."