Peer Review File
Article information: https://dx.doi.org/10.21037/jgo-24-613

Reviewer A

Here the authors presented a case of a 50-year-old Chinese woman with BCLC-C large hepatocellular carcinoma (HCC), obtaining a long-term survival after hepatic arterial infusion chemotherapy (HAIC) followed by transarterial chemoembolization (TACE) combined camrelizumab and apatinib.

After 3 cycles of HAIC with oxaliplatin, fluorouracil, and leucovorin (HAIC-FOLFOX) plus camrelizumab and apatinib, followed by 2 cycles of TACE plus camrelizumab and apatinib, the efficacy was evaluated as a partial response (PR). Subsequent imaging consultation showed an efficacy evaluation of complete response (CR) per the modified Response Evaluation Criteria in Solid Tumors (RECIST). The patient did not experience any serious adverse events during treatment.

The authors concluded that short-course HAIC followed by TACE combined with camrelizumab and apatinib for large HCC is safe and effective.

This is a nice case report of potential clinical impact. However, some issues need to be addressed. 1) transarterial treatments are not recommended as first treatment choice for BCLC-C HCC by current international guidelines due to the risk of liver function deterioration. However, systemic treatments as first-line treatment, thanks to a treatment response, might make the tumor suitable for transarterial treatments. The authors should describe why they started with HAIC, 2) Of interest, the authors reported that following TACE, the tumor microenvironment exhibits a significant enrichment of triggering receptor expressed on myeloid cells 2+ tumor-associated

macrophages (TREM2+ TAMs). This might support the use of TACE session(s) with systemic immunotherapy. In this regard, it has been recently demonstrated that trnasient hypertransaminasemia after conventional TACE is significantly related with objective radiological response thus representing a simple tool to guide treatment strategy of HCC patients in a tailored approach (J Pers Med. 2021 Oct 17;11(10):1041. doi: 10.3390/jpm11101041.). Could the authors provide transaminase serum levels after TACE in this patient and discuss the importance of prognostic tool to guide TACE treatment strategy as recently demonstrated?

-The authors should recall and discuss the growing number of clinical trials evaluating efficacy and safety of combined treatment with immune checkpoint inhibitors to obtain a higher objective radiological response and improved overall survival as recently described in a comprehensive review (Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162.).

The authors would like to express their gratitude to you for your very helpful suggestions to improve this manuscript.

Comment 1: 1) transarterial treatments are not recommended as first treatment choice for BCLC-C HCC by current international guidelines due to the risk of liver function deterioration. However, systemic treatments as first-line treatment, thanks to a treatment response, might make the tumor suitable for transarterial treatments. The authors should describe why they started with HAIC.

Reply 1: The authors have added the following paragraph as advised: Due to the presence of a fistula between the hepatic artery and the middle hepatic vein at baseline, TACE could not be administered in accordance with clinical guidelines(7). Based on a thorough literature review and obtaining informed consent from the patient, we selected HAIC-FOLFOX as the interventional treatment regimen with the aim of achieving tumor response and additional clinical benefits for the patient(8).

Changes in the text: Page 5, line 118-123.

Comment 2: 2) Of interest, the authors reported that following TACE, the tumor microenvironment exhibits a significant enrichment of triggering receptor expressed on myeloid cells 2+ tumor-associated macrophages (TREM2+ TAMs). This might support the use of TACE session(s) with systemic immunotherapy. In this regard, it has been recently demonstrated that trnasient hypertransaminasemia after conventional TACE is significantly related with objective radiological response thus representing a simple tool to guide treatment strategy of HCC patients in a tailored approach (J Pers Med. 2021 Oct 17;11(10):1041. doi: 10.3390/jpm11101041.). Could the authors provide transaminase serum levels after TACE in this patient and discuss the importance of prognostic tool to guide TACE treatment strategy as recently demonstrated?

Reply 2: The authors have added the following paragraph as advised: As illustrated in Figure 1, the patient's serum transaminase levels gradually decreased to within the normal range following cTACE. This result suggests that when using transaminase levels post-TACE to predict objective response rates, it may be necessary to also consider the potential impact of systemic therapy and/or other interventional treatments(13).

Changes in the text: Page 6, line 167-172.

Comment 3: The authors should recall and discuss the growing number of clinical trials evaluating efficacy and safety of combined treatment with immune checkpoint inhibitors to obtain a higher objective radiological response and improved overall survival as recently described in a comprehensive review (Expert Rev Anticancer Ther. 2023 Mar;23(3):279-291. doi: 10.1080/14737140.2023.2181162.).

Reply 3: The authors have added the following paragraph as advised: Furthermore, clinical trials are needed to explore the impact of various combinations of tyrosine kinase inhibitors (TKIs), ICIs, HAIC and TACE on patient objective response rates and survival benefits(18).

Changes in the text: Page 7, line 200-202.

Reviewer B

This is an interesting case with complete remission and long-term survival achieved through a multimodal approach, including Camrelizumab (a PD-1 inhibitor) plus Apatinib (a VEGFR-2 inhibitor), HAIC-FOLFOX, and TACE. This case can potentially provide valuable insights for journal readers, particularly regarding the use of a systemic and liver-directed multimodal approach for HCC with tumor thrombus, without extrahepatic spread.

Minor:

1. Was the HCC confirmed by biopsy? If not, clarify that it was classified as Li-RADS 5 with radiographic confirmation of HCC, and mention that a biopsy was omitted.
2. At the initial diagnosis, was there baseline pelvic/chest imaging to rule out extrahepatic spread?
3. 'Line 35. modified Response Evaluation Criteria in Solid Tumors (RECIST)' should be changed to 'mRECIST'
4. ' Line 102: the patient’s lesions were evaluated 102 as a partial response' by what criteria? 'mRECIST'?

Major:

1. The main differentiating point of this case report, compared to TRIPLET therapy, is the addition of TACE to the HAIC-FOLFOX/ICI/anti-VEGF regimen. The authors should focus on this aspect in the discussion. I recommend rephrasing the current content to emphasize the significance of adding TACE to the TRIPLET regimen.
2. Please include the EMERALD-1 trial (NCT03778957), a Phase 3 study that adds ICI

(anti-PD-L1) plus Bevacizumab (anti-VEGF). This emerging Phase 3 data is relevant to this clinical space, as the systemic component of EMERALD-1 with ICI and anti-VEGF is similar to the combination of camrelizumab and apatinib.

The authors are very thankful to you for taking your valuable time to read this article and for the very helpful suggestions for improvement.

Comment: Was the HCC confirmed by biopsy? If not, clarify that it was classified as Li-RADS 5 with radiographic confirmation of HCC, and mention that a biopsy was omitted.

Reply: The authors have added the following paragraph as advised: The patient was diagnosed with primary HCC in accordance with the 2017 Edition of the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China(7).

Changes in the text: Page 4-5, line 109-111.

Comment: At the initial diagnosis, was there baseline pelvic/chest imaging to rule out extrahepatic spread?

Reply: The authors have added the following paragraph as advised: Chest CT ruled out thoracic tumor metastasis, and no additional evidence of extrahepatic disease was identified.

Changes in the text: Page 4, line 107-109.

Comment: 'Line 35. modified Response Evaluation Criteria in Solid Tumors (RECIST)' should be changed to 'mRECIST'

Reply: The authors have revised the manuscript as suggested.

Changes in the text: Page 2, line 55.

Comment: ' Line 102: the patient's lesions were evaluated 102 as a partial response' by what criteria? 'mRECIST'?

Reply: The authors have added the following paragraph as advised: the patient achieved partial response (PR) according to the mRECIST criteria.

Changes in the text: Page 5, line 125-127.

Comment: The main differentiating point of this case report, compared to TRIPLET therapy, is the addition of TACE to the HAIC-FOLFOX/ICI/anti-VEGF regimen. The authors should focus on this aspect in the discussion. I recommend rephrasing the current content to emphasize the significance of adding TACE to the TRIPLET regimen.

Reply: The authors have added the following paragraph as advised: This case report demonstrated a numerically longer PFS compared to the TRIPLET study regimen. One

possible explanation is the addition of TACE, which may have enhanced local tumor control.
Changes in the text: Page 6, line 159-161.

Comment: Please include the EMERALD-1 trial (NCT03778957), a Phase 3 study that adds ICI (anti-PD-L1) plus Bevacizumab (anti-VEGF). This emerging Phase 3 data is relevant to this clinical space, as the systemic component of EMERALD-1 with ICI and anti-VEGF is similar to the combination of camrelizumab and apatinib.
Reply: The authors have added the following paragraph as advised: The results of the EMERALD-1 study (NCT03778957) further support the PFS benefit of combining TACE with ICI and anti-angiogenic agents in the treatment of HCC(13).
Changes in the text: Page 6, line 165-167.

Reviewer C

This case report provides a valuable example of successful multidisciplinary treatment for unresectable hepatocellular carcinoma, likely related to the FOHAIC-1 trial.

With some additional context and revisions, the content could be made more accessible to readers.

In this case, it was mentioned that no biomarkers were measured. Predictive factors of prognosis from treatment are particularly important in cancer immunotherapy. While the FOHAIC-1 trial did not yield significant results in this regard, further discussion on current and future treatment effect predictions would be beneficial.
Although a long-term complete clinical response was ultimately achieved, scar tissue was observed on imaging. It seems necessary to explain the decision not to perform surgery when assessing downstaging from treatment.

The authors are very thankful to you for taking your valuable time to read this article, for your kind words of affirmation, and for the very helpful suggestions for improvement.
Comment: In this case, it was mentioned that no biomarkers were measured. Predictive factors of prognosis from treatment are particularly important in cancer immunotherapy. While the FOHAIC-1 trial did not yield significant results in this regard, further discussion on current and future treatment effect predictions would be beneficial.

Reply: The authors have added the following paragraph as advised: Currently, there are no reliable predictive biomarkers for assessing the efficacy of HAIC combined with ICI, TKI, and TACE in the treatment of advanced large hepatocellular carcinoma(10,18). Based on the results and hypotheses presented in this study, monitoring immune cell populations and PD-L1 expression within the immune microenvironment before and after treatment may represent a potential direction for future research.
Changes in the text: Page 7, line 191-196.

Comment: Although a long-term complete clinical response was ultimately achieved, scar tissue was observed on imaging. It seems necessary to explain the decision not to perform surgery when assessing downstaging from treatment.
Reply: The authors have added the following paragraph as advised: We recommended an evaluation of the patient's eligibility for surgical resection, however, the patient declined due to financial constraints.
Changes in the text: Page 5, line 134-136.

Reviewer D

The title of the article suggests complete response (but this needs to be clarified, so as not to give an erroneous impression because by RECIST criteria this patient achieved a partial response but a complete response by mRECIST only).
Reply: Dear Reviewer, the authors had referenced the use of "complete response" in the titles of several articles related to hepatocellular carcinoma to avoid an overly long title for the manuscript (PMID: 39076997, PMID: 37869012, PMID: 33738601 and PMID: 31730491).
Changes in the text: None.

Would modify conclusion about this approach being safe and affective since this is just 1 case report.
Reply: The authors have revised the Conclusions as advised: HAIC combined with TACE, camrelizumab, and apatinib may represent a viable treatment approach for large and advanced hepatocellular carcinoma, particularly in patients achieving complete response, which may indicate the potential for long-term survival. More clinical studies need to be initiated to explore and validate the efficacy and safety of this treatment modality.
Changes in the text: Page 9, line 264-268.

Would modify key findings in highlighted box with regards to long term survival as

this conclusion can not be made based on 1 case report.

Reply: The authors have revised the Key findings as advised: HAIC combined with TACE, camrelizumab, and apatinib may represent a viable treatment approach for large and advanced hepatocellular carcinoma, particularly in patients achieving complete response, which may indicate the potential for long-term survival.

Changes in the text: Page 3, Key findings