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Hepatic artery infusion of FOLFOX chemotherapy plus camrelizumab combined with sorafenib for advanced hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (Double-IA-001): a phase II trial

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Abstract

Background Hepatic arterial infusion chemotherapy (HAIC) with a combination of oxaliplatin, fluorouracil, and leucovorin (FOLFOX) has shown excellent local control for patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC). In China, both camrelizumab (a programmed cell death-1 [PD-1] inhibitor) and sorafenib have been approved for the first-line treatment of advanced HCC. This study aimed to investigate the efficacy and safety of hepatic artery infusion of FOLFOX chemotherapy plus camrelizumab combined with sorafenib in BCLC stage C advanced HCC.

Methods This was a single-arm phase II trial (ChiCTR2100041874) with a Simon's two-stage design. Eligible patients were given a maximum of 6 cycles of hepatic artery infusion with FOLFOX chemotherapy plus camrelizumab (200 mg once every 3 weeks). Sorafenib (400 mg orally twice daily) was given since day 3 after the completion of the first cycle of hepatic artery infusion until disease progression, intolerable toxicity, or conversion to surgical resection. The primary endpoint was objective response rate (ORR) based on the modified Response Evaluation Criteria In Solid Tumors (mRECIST).

Results Between January 4, 2021, and December 11, 2023, 25 patients were enrolled. Eleven patients had partial response, with an ORR of 44.0% (95% CI, 24.6–63.5%). The primary endpoint was not met, and the study failed to enter the second stage. Median progression-free survival was 4.87 months (95% CI, 2.07–7.66), with a 12-month rate of 23.2%. Median overall survival was 8.87 months (95% CI, 8.17–9.57), with 12- and 24-month rates of 40.3% and 26.9%, respectively. Two (8.0%) patients received curative resection after the study treatment. Grade ≥ 3 treatment-related adverse events occurred in 19 (76.0%) patients, with the most common being decreased lymphocyte count (13 [52.0%]), increased aspartate aminotransferase (11 [44.0%]), and increased alanine aminotransferase (seven [28.0%]).

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Conclusions Hepatic artery infusion of FOLFOX chemotherapy plus camrelizumab combined with oral sorafenib shows manageable safety profile but modest antitumor activity in patients with BCLC stage C advanced HCC.

Keywords Hepatocellular carcinoma, Hepatic artery infusion, FOLFOX, Camrelizumab, Sorafenib, Phase II trial

Background

Hepatocellular carcinoma (HCC) ranks the sixth most common tumor and the third most lethal malignant tumor worldwide, with over 780,000 new cases and more than 740,000 deaths annually [1]. Advanced HCC accounts for approximately 40% of all newly diagnosed cases [2]. In the natural course of the disease, the expected median survival is 6 months, and the 1-year survival rate is 25% [3].

Historically, advanced HCC lacked effective treatment methods. The SHARP study and ORIENTIAL trials confirmed that sorafenib can prolong the overall survival (OS) of patients with advanced HCC by 2.8 months compared to placebo [4, 5]. Subsequently, sorafenib has been recommended as the standard first-line treatment by several guidelines since 2007 [6].

In 2018, hepatic arterial infusion chemotherapy (HAIC) with a combination of oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) is demonstrated effective in the control of advanced HCC, with an objective response rate (ORR) of 28.6% [7]. On this basis, He et al. conducted a multicenter, open-label randomized controlled trial comparing HAIC with FOLFOX regimen plus oral sorafenib to sorafenib monotherapy [8]. The results showed that the combination group significantly prolonged median OS (13.37 months vs 7.13 months) and progression-free survival (PFS; 7.03 months vs 2.6 months) compared to sorafenib group. This study indicates that tyrosine kinase inhibitor (TKI) combined with HAIC is an effective treatment strategy for patients with advanced HCC.

Immunotherapy has emerged as a major breakthrough in the field of cancer treatment [9]. Many studies showed that the targeted therapy can have a synergistic effect with anti-programmed cell death-1 (PD-1) antibody [7, 10], thereby promoting anti-tumor immunity and prolonging patient survival. A recent clinical trial combining camrelizumab (anti-PD-1 antibody) and apatinib for the treatment of advanced HCC reported an ORR of 50% and a disease control rate (DCR) of 93.8% [11]. In clinical practice, anti-PD-1 antibodies are mainly administered intravenously. Several previous studies explored the clinical efficacy of arterial infusion of anti-PD-1 antibody for melanoma, which showed positive efficacy and acceptable safety [12, 13]. In theory, hepatic arterial infusion of FOLFOX chemotherapy plus camrelizumab combined with oral sorafenib can further improve the efficacy of immunotherapy in the body.

Therefore, we conducted a phase II trial to investigate hepatic artery infusion of FOLFOX chemotherapy plus camrelizumab combined with oral sorafenib for patients with Barcelona Clinic Liver Cancer (BCLC) stage C advanced HCC.

Methods

Study design and patients

Double-IA-001 study was a single-arm clinical trial. The key inclusion criteria included the following: [1] newly diagnosed and pathological confirmed HCC; [2] surgically unresectable disease; [3] at least one measurable liver lesion; [4] Barcelona Clinic Liver Cancer (BCLC) stage C disease; and [5] Eastern Cooperative Oncology Group performance status 0 or 1. The key exclusion criteria included the following: [1] Child–Pugh class C; [2] presence of massive ascites, gastric esophageal varices, or upper gastrointestinal bleeding within 1 year; [3] brain or bone metastases that required immediate surgery or radiotherapy; [4] history of autoimmune diseases. The detailed eligibility criteria can be found in the protocol.

All patients provided their written consent prior to enrollment. The study protocol was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (B2020-230–01). The study is registered with ChiCTR.org.cn, ChiCTR2100041874.

Procedures

After enrollment, patients received up to six 21-day cycles of hepatic arterial infusion with camrelizumab and FOLFOX chemotherapy. The infusion of camrelizumab (200 mg in 100 mL 0.9% saline) was administered at a constant rate for a total of 2 h. The FOLFOX regimen consisted of oxaliplatin 85 mg/m^2 at a constant rate for 1.5 h, followed by leucovorin 200 mg/m^2 for 1.5 h, and fluorouracil 2500 mg/m^2 for 46 h. In addition, all patients received sorafenib (400 mg orally twice daily, beginning since day 3 after initiation of hepatic arterial infusion) until disease progression or unacceptable toxicity. Patients whose disease was successfully downstaged after the study treatment had the option to receive surgical resection or ablation (for BCLC stage A disease), or transarterial chemoembolization (TACE; for BCLC stage B disease). For patients who did not achieve downstage after six cycles of combination treatment, intravenous infusion of camrelizumab every 3 weeks and sorafenib were recommended for maintenance treatment.

Hepatic arterial infusion was performed by inserting a 5-French Yashiro catheter (Terumo Corporation, Tokyo, Japan) through the femoral artery. After arteriography of major artery supplying the liver, a 2.7-French microcatheter was then advanced to the tumor-feeding artery. When a tumor demonstrated additional blood supply from extrahepatic sources, the catheter tip was positioned in the main feeding artery. If the distance between the proper hepatic artery and gastroduodenal artery was close (< 1 cm), coils were utilized for vascular embolization of gastroduodenal artery. After the completion of hepatic arterial infusion, the catheter and sheath were removed.

Follow-up and endpoints assessment

Patients were followed every 3 weeks during the study treatment. Tumor response was assessed by two experienced radiologists using contrast-enhanced magnetic resonance imaging or computed tomography every 2 cycles.

The primary endpoint was ORR (defined as the proportion of patients with the best overall response of complete response [CR] or partial response [PR]) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[14]. Secondary endpoints included ORR per RECIST version 1.1, PFS, OS, and safety. PFS was defined as the time from the start of study treatment to disease progression or death from any cause. OS was defined as the time from the start of study treatment to death from any cause.

Adverse events (AEs) occurred were graded according to the Nation Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [15].

Statistical analysis

An optimal Simon's 2-stage design was adopted in this study, with a one-sided α level of 5% and a power over 90% [16]. The null hypothesis of ORR by mRECIST was 40.0%, and the alternative hypothesis was 60.0%. If over 12 out of the initial 25 evaluated patients had objective response during the first stage, additional 41 patients would be recruited. Otherwise, the study would be terminated. Overall, the study treatment would be deemed worthy of further investigation if more than 32 of 66 patients responded.

All patients who enrolled were included for both efficacy and safety analyses. ORR and post hoc DCR were expressed as percentages, with 95% confidence intervals (CIs) calculated using the Clopper-Pearson method. PFS, OS, and post hoc liver-specific PFS, time to response (TTP), and duration of response (DoR) were estimated using the Kaplan–Meier method, and their 95% CIs were calculated using the Brookmeyer-Crowley method. All statistical analyses were carried out using R 4.2.2 (The R Foundation for Statistical Computing, 2022).

Results

Patient characteristics

From January 4, 2021, to December 11, 2023, a total of 25 patients were enrolled (Fig. 1). The study was prematurely terminated because the primary endpoint was not met in the first stage. The baseline characteristics of the enrolled patients in the first stage are listed in Table 1. The median age was 48 years (range, 34–67). The majority patients were male (96.0%), had hepatitis B virus infection (92.0%), large tumor size (≥ 10 cm; 60.0%), multiple intrahepatic tumors (≥ 4, 80.0%), and portal vein

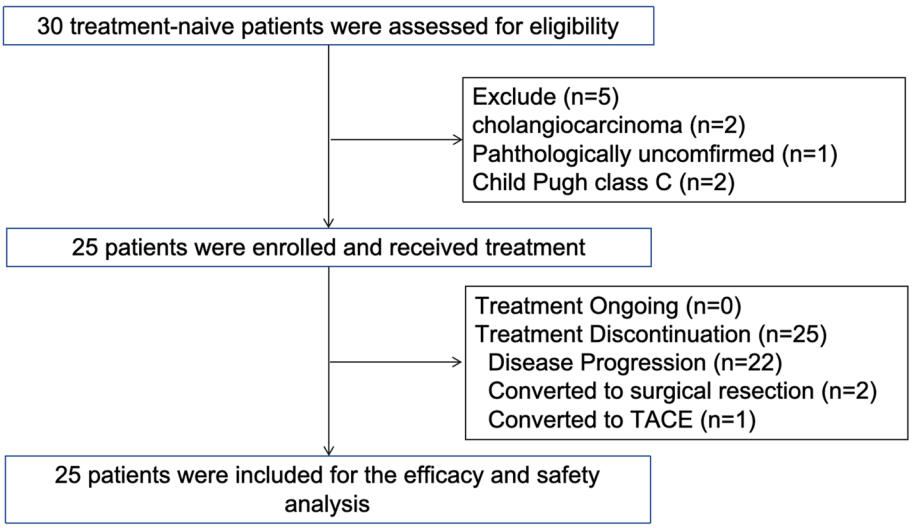

Fig. 1 Patient flowchart

Table 1 Baseline characteristics of patients

Variables	Values/number (*n* = 25)
Age, years, median (range)	48 (34–67)
< 50	13 (52.0%)
≥ 50	12 (48.0%)
Gender	
Male	24 (96.0%)
Female	1 (4.0%)
Etiology	
HBV	23 (92.0%)
HCV	1 (4.0%)
Others	1 (4.0%)
ECOG performance score	
0	19 (76.%)
1	6 (24.0%)
Child–Pugh Score	
5	20 (80.0%)
6	2 (8.0%)
7	2 (8.0%)
8	1 (4.0%)
ALBI grade	
Grade 1	17 (68.0%)
Grade 2	7 (28.0%)
Grade 3	1 (4.0%)
AFP	
< 200	9 (36.0%)
≥ 200	16 (64.0%)
Tumor size, cm	
< 10	10 (40.0%)
≥ 10	15 (60.0%)
Tumor number	
< 4	5 (20.0%)
≥ 4	20 (80.0%)
PVTT	
Vp2	1 (4.0%)
Vp3	8 (32.0%)
Vp4	9 (36.0%)
Absent	7 (28.0%)
IVCTT	
Hepatic vein invasion	3 (12.0%)
IVC invasion	1 (4.0%)
Absent	21 (84.0%)
Extrahepatic metastasis	
Present	3 (12.0%)
Absent	22 (88.0%)

HBV hepatitis B virus; *HCV* hepatitis C virus; *ECOG* Eastern Cooperative Oncology Group; *ALBI* albumin-bilirubin; *AFP* alpha-fetoprotein; *PVTT* portal vein tumor thrombus; *IVCTT* inferior vena cava tumor thrombus

tumor thrombosis (72.0%). A total of 12 (48.0%) subjects were at a high-risk (presence of Vp-4 portal vein tumor thrombosis and/or tumor occupancy of 50% of the liver).

The median cycles of study treatment was 3 (range, 1–6). Of the five patients who completed 6 cycles of study treatment, the median cycles of camrelizumab maintenance treatment were 5 (range, 1–12), and the median duration of sorafenib treatment was 3.6 months (range, 1.0–20.0). Treatment dose reduction and discontinuation are shown in Additional file 1–2 (Table S1 and Table S2). As of July 31, 2024, the median duration of follow-up was 26.70 months (95% CI, 9.82–43.7).

Efficacy

Of the 25 patients enrolled in the first stage, 11 patients had a confirmed PR by mRECIST, with an ORR of 44.0% (95% CI, 24.6–63.5%). Because the ORR by mRECIST did not reach the threshold, the study failed to proceed to the second stage. Median TTR was 1.83 months (95% CI, 2.10–2.89), and the median DoR was 8.43 months (95% CI, 1.09–15.78). Based on RECIST 1.1, nine patients had a confirmed PR, and the ORR was 36.0%. The DCR was 64.0% by either of these two criteria (Table 2 and Fig. 2). In high-risk subgroup, the ORR and DCR were 41.7% and 58.3% by either of these two criteria, respectively.

Based on mRECIST, the median PFS was 4.87 months (95% CI, 2.07–7.66), with the 6-, 12-, and 24-month PFS rates of 38.8%, 23.2%, and 15.5%, respectively. Median liver-specific PFS was 5.47 months (95% CI, 2.20–8.74). The patterns of progression were listed in Additional file 3: Table S3. Median OS was 8.87 months (95% CI, 8.17–9.57) (Fig. 3), with the 6-, 12-, and 24-month OS rates of 64.0%, 40.3%, and 26.9%, respectively. After the study treatment, two (8.0%) of 25 patients received curative resection. One (4.0%) patient received TACE combined with hepatic arterial infusion of camrelizumab and oral sorafenib after 6 cycles of study treatment.

Safety

The most frequent treatment-related AEs (TRAEs) included increased aspartate aminotransferase (25 [100%]), decreased lymphocyte count (24 [96.0%]), increased alanine aminotransferase (22 [88.0%]), hypoalbuminemia (22 [88.0%]), anemia (20 [80.0%]), increased blood bilirubin (18 [72.0%]), decreased platelet count (15 [60.0%]), hyperglycemia (15 [60.0%]), hand-foot syndrome (14 [56.0%]), and fatigue (14 [56.0%]; Table 3). TRAEs of grade ≥3 were observed in 19 (76.0%) patients, with the predominant events being decreased lymphocyte count (13 [52.0%]), increased aspartate aminotransferase (11 [44.0%]), and increased alanine aminotransferase (seven [28.0%]). Hypertension events were reported in six (24.0%) patients, all of which were

Table 2 Tumor response ($n = 25$)

Variables	mRECIST ($n = 25$)	RECIST 1.1 ($n = 25$)
Best objective response		
Complete response	0 (0.0%)	0 (0.0%)
Partial response	11 (44.0%)	9 (36.0%)
Stable disease	5 (20.0%)	7 (28.0%)
Progressive disease	9 (36.0%)	9 (36.0%)
Objective response rate, *n* %	11 (44.0%)	9 (36.0%)
Disease control rate, *n*,%	16 (64.0%)	16 (64.0%)
TTR, months, median (95% CI)	1.83 (1.40–2.27)	1.73 (1.44–2.03)
DOR, months, median (95% CI)	8.43 (1.09–15.78)	6.90 (2.73–11.07)
PFS, months, median (95% CI)	4.87 (2.07–7.66)	4.33 (2.07–6.60)
6-month PFS rate	38.8%	34.7%
12-month PFS rate	23.3%	24.0%
Liver-specific PFS, months, median (95% CI)	5.47 (2.20–8.74)	4.87 (2.09–7.65)
6-month PFS rate	42.9%	34.7%
12-month PFS rate	22.7%	24.0%
18-month PFS rate	22.7%	24.0%

TTR time to response; *DOR* duration of response; *PFS* progression-free survival

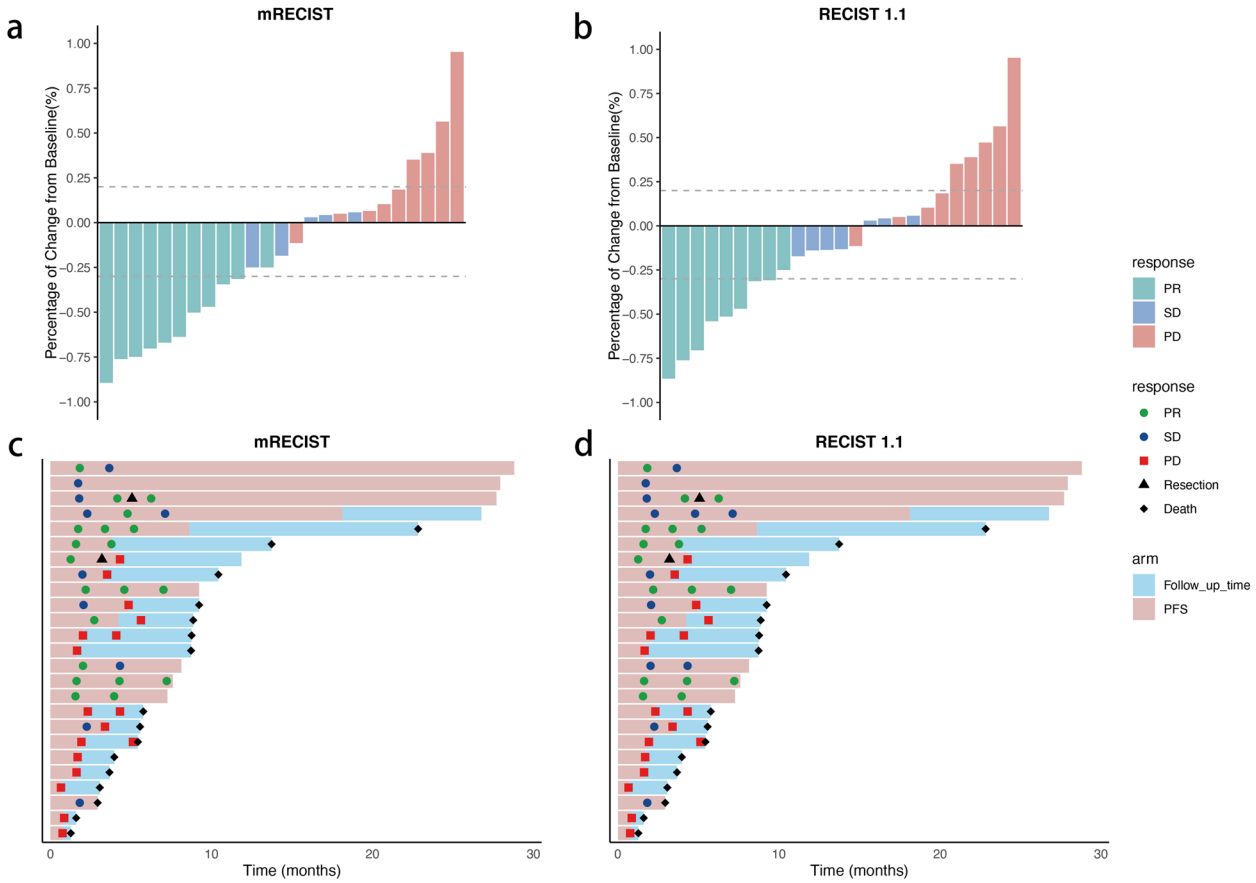

Fig. 2 Treatment response and duration. **a** Best percent change from baseline in target lesions per mRECIST. **b** Best percent change from baseline in target lesions per RECIST 1.1. **c** Treatment exposure and response duration per mRECIST. **d** Treatment exposure and response duration per RECIST 1.1

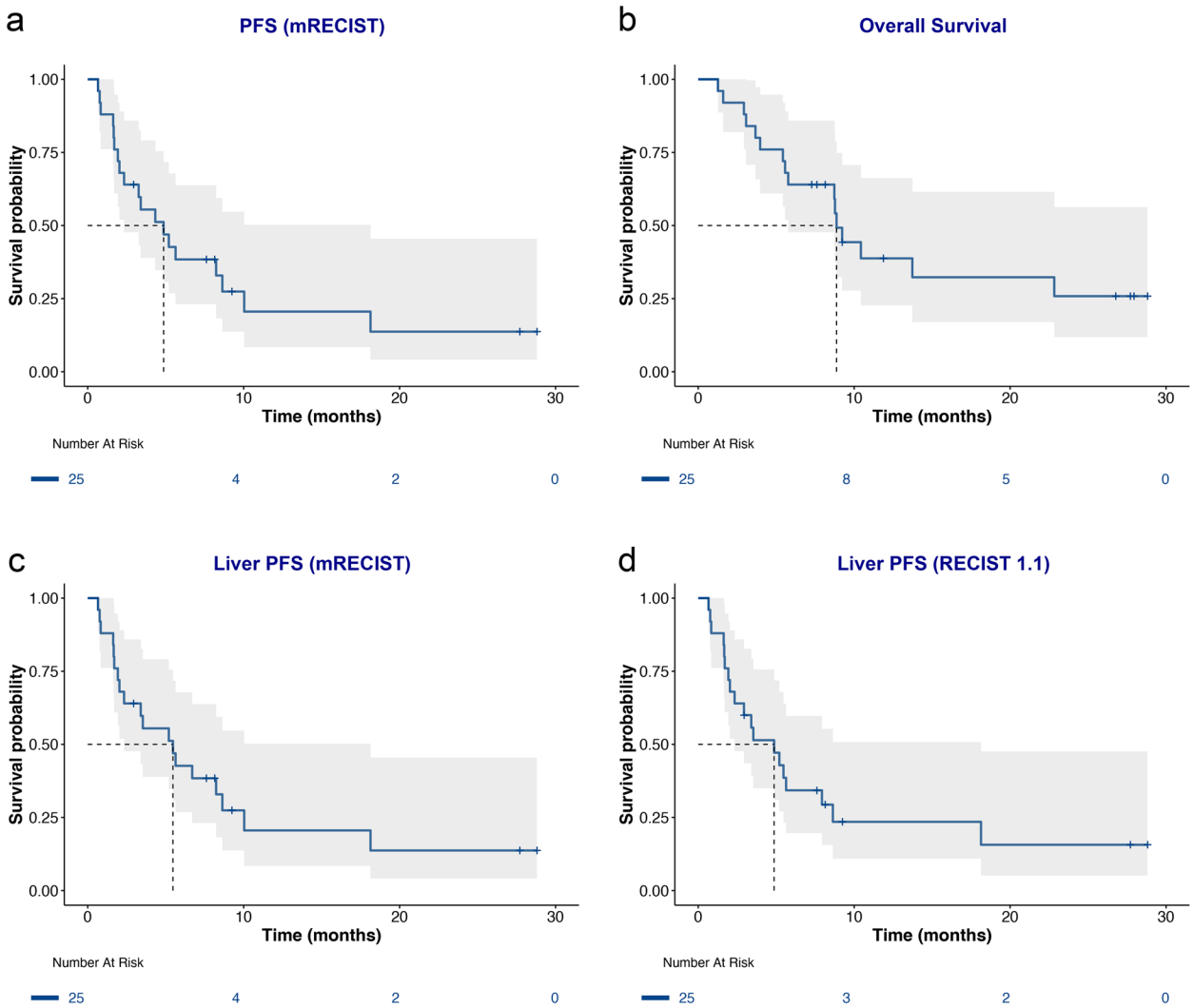

Fig. 3 Survival analysis. **a** Kaplan–Meier survival curves of progression-free survival (PFS) per mRECIST. **b** Kaplan–Meier curves of overall survival. **c** Kaplan–Meier curves of liver-specific PFS per mRECIST. **d** Kaplan–Meier curves of liver-specific PFS per RECIST 1.1

related to sorafenib and mostly (5/6) were grades 1 and 2. Reactive cutaneous capillary endothelial proliferation was observed in only one (4.0%) patient, which is mild. Regarding the intra-arterial infusion of camrelizumab, no adverse effects or acute phase responses were observed during the infusion period. AEs led to dose reduction in one (4.0%) patient, and no patients discontinued treatment due to AEs. No patients experienced immune-related serious AEs.

Discussion

Double-IA-001 trial failed to meet the primary endpoint, showing an ORR of 44% by mRECIST. However, this was the first prospective study to assess hepatic arterial infusion of PD-1 blockade (camrelizumab) combined with HAIC and oral sorafenib in the treatment of BCLC stage C advanced HCC, which demonstrated the safety of hepatic arterial infusion of immune checkpoint inhibitor, with no identified immune-related serious AEs.

The Double-IA-001 trial was conceived and designed in 2020, during the period when sorafenib and lenvatinib represented the standard first-line targeted therapies for advanced stage HCC [17]. Given the substantial cost of lenvatinib in mainland China and the demonstrated efficacy of FOLFOX-HAIC combined with sorafenib in the study by He et al. [8], we selected sorafenib as the targeted therapy for this clinical trial. Compared with the previous study by He et al., the ORR of the triplet combination in our study was slightly higher than that of HAIC combined with sorafenib (40.8%). It is worth

Table 3 Treatment-related adverse effects of all grades

Categories	Any grade	Grades 1 and 2	Grade 3 or higher
Aspartate aminotransferase increased	25 (100.0%)	14 (56.0%)	11 (44.0%)
Alanine aminotransferase increased	22 (88.0%)	15 (60.0%)	7 (28.0%)
Hypoalbuminemia	22 (88.0%)	22 (88.0%)	0 (0.0%)
Neutrophil count decreased	11 (44.0%)	9 (36.0%)	2 (8.0%)
Lymphocyte count decreased	24 (96.0%)	11 (44.0%)	13 (52.0%)
Anemia	20 (80.0%)	17 (68.0%)	3 (12.0%)
Platelet count decreased	15 (60.0%)	10 (40.0%)	5 (20.0%)
Blood bilirubin increased	18 (72.0%)	13 (52.0%)	5 (20.0%)
Proteinuria	9 (36.0%)	9 (36.0%)	0 (0.0%)
Abdominal pain	7 (28.0%)	7 (28.0%)	0 (0.0%)
White blood cell decreased	10 (40.0%)	6 (24.0%)	(16.0%)
Anorexia	8 (32.0%)	8 (32.0%)	0 (0.0)
Hyperglycemia	15 (60.0%)	15 (60.0%)	0 (0.0%)
Hyperuricemia	11 (44.0%)	11 (44.0%)	0 (0.0%)
Hypokalemia	10 (40.0%)	10 (40.0%)	0 (0.0%)
Rash	1 (4.0)	1 (4.0)	0 (0.0)
Hypertension	6 (24.0%)	5 (20.0%)	1 (4.0%)
Hand-foot syndrome	14 (56.0%)	13 (56.0%)	0 (0.0)
RCCEP	1 (4.0%)	1 (4.0%)	0 (0.0%)
Diarrhea	2 (8.0%)	2 (8.0%)	0 (0.0%)
Vomiting	2 (8.0%)	2 (8.0%)	0 (0.0%)
Fatigue	14 (56.0%)	14 (56.0%)	0 (0.0%)
Hematuria			
Upper respiratory infection	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gingival hemorrhage	5 (20.0%)	5 (20.0%)	0 (0.0%)
Fever	6 (24.0%)	6 (24.0%)	0 (0.0%)
Oral mucositis	5 (20.0%)	5 (20.0%)	0 (0.0%)
Gingivitis	5 (20.0%)	5 (20.0%)	0 (0.0%)
Ascites	4 (16.0%)	0 (0.0%)	0 (0.0%)
Epistaxis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cough	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)

noting that 12.0% of the patients included in our study had Child–Pugh B liver function at diagnosis, which partially explains the unsatisfied efficacy. The SHARP trial also enrolled a small proportion of patients with Child–Pugh B liver function, suggesting the potential benefits [5]; in clinical practice, manageable toxicity was observed among this patient group receiving PD-1 blockade therapy. Therefore, patients with Child–Pugh B liver function was not excluded in the trial. Compared with the reported data by He et al., the incidence of grade 3 or 4 TRAEs in our study was similar. Although this regimen cannot be recommended as standard of care, our results suggest that for patients who are willing to incorporate immunotherapy into the treatment, our treatment regimen maybe an alternative option. Further optimization of drug combinations or dosing strategies is required to further improve the current regimen.

In 2023, Zhang et al. reported the efficacy of the triplet combination of HAIC with FOLFOX regimen, intravenous camrelizumab, and oral apatinib for BCLC stage C advanced HCC in a phase II trial [18]. According to mRECIST, the ORR of their trial reached 88.6%, and the median PFS was 9.53 months, which was higher than the results of our study. The differences in ORR between this study and out study may be explained by several possible reasons. First, the efficacy of apatinib is significantly better than sorafenib, and previous phase 3 CARES-310 study proved that the combination of camrelizumab and apatinib had a synergistic antitumor effect in the treatment of advanced HCC[19].

By contrast, there are currently few reports supported the combination of sorafenib and immune checkpoint inhibitors [20]. Second, it is generally believed naive T cells need to differentiate and mature in peripheral lymph nodes before entering the tumor microenvironment via microcirculation to exert their tumor-killing effects [21, 22]. Although our trial innovatively explored the safety and efficacy of hepatic arterial infusion of PD-1 antibody and demonstrated its safety, the arterial perfusion of PD-1 antibodies can only ensure higher local antibody concentrations within the tumor, while its ability to prime peripheral T-cell responses may be insufficient, thereby leading to limited anti-tumor immunity. Our results suggested that hepatic arterial infusion of anti-PD-1 antibody combined with intravenous anti-PD-1 antibody may overcome the limitation of solely hepatic arterial infusion of anti-PD-1 antibody.

Previous studies suggest that immune cells in the circulation play a crucial role in cancer immunity cycle [23, 24]. Although theoretically the anti-PD-1 antibody infused locally can reflux to the whole body through veins, the results of our study suggests that intravenous PD-1 antibody may be superior to arterial administration as it may better activate the immune cells in the peripheral blood. However, studies comparing the immunological mechanism between arterial administration and intravenous administration of immune checkpoint inhibitors are rare. Our results provided important hints that these two routes of administration might be different. From this perspective, programmed cell death-ligand 1 (PD-L1) is an ideal target on the surface of tumors, and hepatic arterial infusion of anti-PD-L1 antibody may achieve high efficiency and low toxicity [25, 26]. In addition, the use of anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody is always accompanied by significant immune-related side effects [27, 28]. Attempting hepatic arterial infusion of anti-CTLA-4 antibody may also achieve both goals of high efficiency and low toxicity.

Many published studies regard HAIC combined with TKI and ICIs as a homogenous treatment modality for HCC [29–31], while our study present important evidence that the combination should be selected with caution. Based on the current published results on triplet combination treatment (Additional file 4: Table S4), the camrelizumab and apatinib seemed to be the preferred choice, while the combination of toripalimab and lenvatinib is a choice that balanced the effectiveness and safety [32, 33]. More efforts are needed in exploration of the effectiveness of other combinations, including anti-PD-L1 antibody plus bevacizumab, anti-PD-1 antibody plus anti-CTLA4 antibody, etc., in combination with FOLFOX-HAIC for advanced stage HCC patients.

The present study has several limitations. First, the lack of a control arm in our single-arm design precludes definitive attribution of the observed benefits solely to the addition of systemic therapy following HAIC. Second, the sample size was limited, and we did not meet the predetermined criteria of Simon's two-stage design.

Conclusions

While hepatic artery infusion of FOLFOX chemotherapy plus camrelizumab combined with oral sorafenib demonstrated a manageable safety profile, its antitumor efficacy was limited in advanced HCC.

Abbreviations

HAIC	Hepatic arterial infusion chemotherapy
BCLC	Barcelona Clinic Liver Cancer
HCC	Hepatocellular carcinoma
PD-1	Programmed cell death-1
ORR	Objective response rate
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
DCR	Disease control rate
TACE	Transarterial chemoembolization
CR	Complete response
PR	Partial response
AE	Adverse event
CI	Confidence interval
PFS	Progression-free survival
OS	Overall survival
TTP	Time to response
DoR	Duration of response

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04110-1.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions

Conception and design: LS, FC, YL, GN, WF; Data analysis and interpretation: LS, LL, HT, CW, YW, SC, HZ, LX; Resources: LS, WF; Funding acquisition: FC; Writing-original draft: LS, FC, YL, GN; Writing-review & editing: All authors. Final approval of manuscript: All authors. LS and WF were responsible for the study design. FC, YL, GN have accessed and verified the data. WF is responsible for the decision to submit the manuscript. All authors read and approved the final manuscript.

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Data availability

The authenticity of this data has been validated by uploading the critical raw data onto the Research Data Deposit public platform (www.researchdata.org.cn).

Declarations

Ethics approval and consent to participate

Ethical approval for the trial was granted by the Institutional Review Board of the Sun Yat-sen University Cancer Center (B2020-230–01). All participants provided written consent to be involved in the study.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

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