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RESEARCH

Hepatic arterial infusion chemotherapy combined with systemic therapy sequentially or simultaneously for advanced hepatocellular carcinoma

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Abstract

Background and aims The goal of this study was to compare the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) combined with targeted therapy and PD-(L)1 blockade (triple therapy), either sequentially (SE) or simultaneously (SI), in the treatment of Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC).

Approach and results From January 1, 2018, to June 1, 2022, 575 patients with BCLC stage C HCC who underwent SE or SI triple therapy were retrospectively enrolled. Propensity score matching (PSM; 1:1) was performed to eliminate possible confounder imbalances across cohorts. We used the Kaplan–Meier method and a log-rank test to compare the overall survival (OS) and progression-free survival (PFS) rates between the SI and SE groups. The tumor response and the incidence of adverse events (AEs) were reported. After PSM, 182 patients in each of the two groups were matched. The median OS in the SI group was significantly longer than that in the SE group (28.8 *vs.* 16.1 months; $P = 0.002$), and the median PFS was significantly improved in the SI *versus* SE group (9.6 *vs.* 7.0 months; $P = 0.01$). The objective response rate based on the mRECIST was higher in the SI group (58% *vs.* 37%; $P < 0.001$). The total incidences of grade 3–4 AEs were 111/182 (60.9%) and 128/182 (70.3%) in the SE and SI groups, respectively. No grade 5 AEs were reported in either group.

Conclusions Simultaneous HAIC plus targeted therapy and PD-(L)1 blockade significantly improved outcomes compared to the sequential regimen in patients with BCLC stage C HCC, with no unexpected AEs.

Clinical relevance statement. The patients who received hepatic arterial infusion chemotherapy combined with targeted therapy and PD-(L)1 blockade simultaneously have a better prognosis than those who received it sequentially.

Keywords Hepatic arterial infusion chemotherapy · Targeted therapy · PD-(L)1 blockade · Hepatocellular carcinoma · Sequentially and simultaneously

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Abbreviations

AEs	Adverse events
AFP	Alpha-fetoprotein
AJCC	American joint Committee on cancer
ALBI	Albumin-bilirubin grade
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence interval
CNLC	China liver cancer staging
CR	Complete response
ECOG	Eastern Cooperative Oncology Group
EHM	Extrahepatic metastasis
HAIC	Hepatic arterial infusion chemotherapy
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICIs	Immune checkpoint inhibitors
mRECIST	Modified Response Evaluation Criteria In Solid Tumors

ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PS	Propensity score
PSM	Propensity score matching
SD	Stable disease
SE	Sequentially
SI	Simultaneously
TACE	Transcatheter arterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is the seventh most prevalent cancer and second most prevalent driver of tumor-associated death globally [1]. At diagnosis, many patients with advanced HCC (aHCC) do not have the option of surgical resection [2]. Previously, treatment with sorafenib and/or lenvatinib was recommended only as first-line treatment for aHCC [3, 4]. The IMbrave150 study demonstrated significantly improved outcomes with bevacizumab and atezolizumab *versus* sorafenib, which initiated an era of combined therapy for aHCC, including angiogenesis inhibitors plus immune checkpoint inhibitors (ICIs). However, the low objective response rate (ORR) for combination regimens limits their ability to improve patients' survival [5–9].

Currently, local therapy, primarily in the form of transcatheter arterial chemoembolization (TACE), represents the first-line choice for aHCC and can improve the ORR. However, researchers have found evidence suggesting a significant risk of TACE failure in patients with high tumor burdens [6, 9]. Another local therapy, hepatic arterial infusion chemotherapy (HAIC), has been shown to significantly improve outcomes over TACE in patients with large unresectable HCC (uHCC) [10, 11]. Indeed, the FOHAIC-1 study showed that HAIC using a targeted regimen of oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) improved the prognoses of patients with aHCC more than sorafenib. Many studies have been conducted to explore the efficacy and safety of HAIC-based combination therapy [12, 13]. Some small-sample studies have demonstrated that HAIC combined with a targeted regimen and programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) blockade (triple therapy) could prolong the overall survival (OS) of patients with aHCC, highlighting its potential to become a first-line treatment [12, 14–19].

Nonetheless, it remains unclear how to administer triple therapy in clinical practice. To date, all studies on triple therapy have used the treatments simultaneously (SI) and reported excellent efficacy. However, high incidences of adverse events (AEs) were also reported in these studies [15–20]. Some physicians have proposed that sequentially (SE) administering HAIC, targeted therapy, and PD-(L)1 blockade might reduce the incidence of AEs while ensuring efficacy, and may even further improve HCC patient prognosis, based on the treatment of other cancers and animal experiments [21–25]. Therefore, we designed and conducted a multicenter retrospective study to compare the safety and efficacy of SE *versus* SI HAIC combined with targeted therapy and PD-(L)1 blockade in the treatment of Barcelona Clinic Liver Cancer (BCLC) stage C HCC, using propensity score matching (PSM) to reduce intercohort basal differences.

Methods

Study design and patients

This retrospective study included patients treated at five high-volume centers in China from January 1, 2018, to June 1, 2022 (Fig. 1A). HCC was confirmed by either histological or radiological assessment based on the Guidelines of the American Association for the Study of Liver Diseases. Cases enrolled in this investigation met the following inclusion criteria: (1) staged as BCLC C; (2) Child–Pugh grade A or B; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and (4) SE or SI administration of triple therapy. The exclusion criteria were as follows: (1) HCC combined with other malignancies; (2) history of systematic treatment, including angiogenesis inhibitors and immune therapy; (3) TACE during HAIC; or (4) incomplete clinical or follow-up data.

The treatment regimen for the study participants was divided into two stages. In the first stage, all patients received two to six HAIC treatments within 18 weeks, with treatment intervals of approximately 3 weeks. In the SE group, the patients received HAIC treatment alone, while the combination of angiogenesis inhibitors and immune therapy was applied in the SI group HAIC. Patients in the SI group received targeted therapy and immunotherapy within 3 weeks after the end of the first HAIC. The number of HAIC cycles and the specific intervals for both groups were determined by the clinical attending physician. In the following situations, HAIC treatment was terminated and transited to the second stage or subsequent-line treatment: (1) disease progression; (2) no longer demonstrating a continuous benefit from HAIC; and (3) presence of intolerable adverse reactions. In the second stage, patients received regular angiogenesis inhibitors and immune therapy until disease progression or intolerable adverse reactions (Fig. 1B).

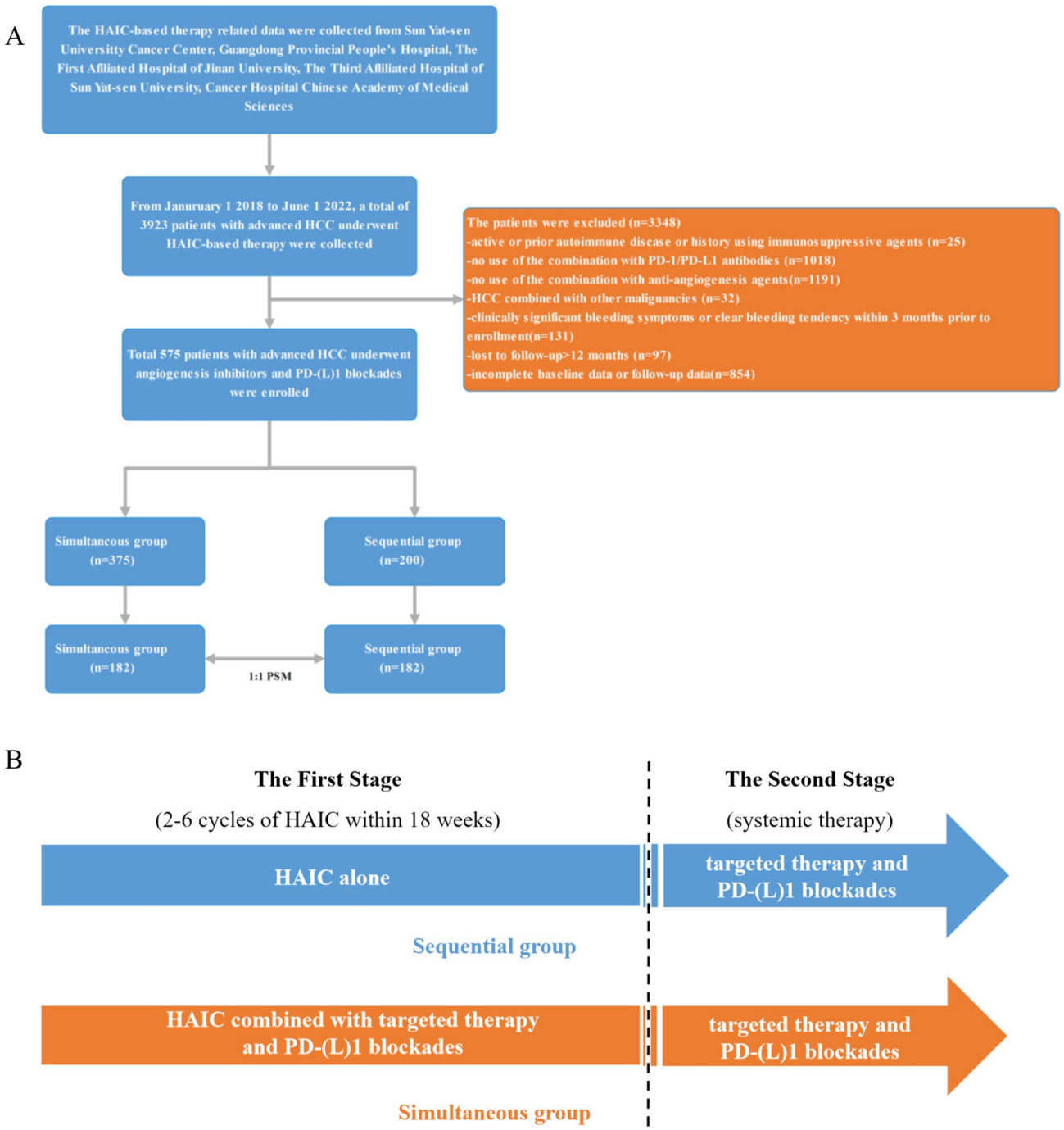

Fig. 1 **A**: flowchart of BCLC stage C HCC patients who received triple therapy; **B**: treatment schedules of sequential and simultaneous group groups. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma

Patients and their families primarily made the treatment decisions based on the recommendations of interventional radiologists and surgeons. We obtained informed consent from all patients before therapy. All patients were routinely assessed for safety and treatment response. This study was reviewed and approved by the Ethics Committee of Sun Yat-Sen University Cancer Center (Guangzhou, China; No. B2023-362–01) and followed the tenets of the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Treatment regimens

Interventional radiologists performed HAIC under the guidance of digital subtraction angiography. The celiac, superior mesenteric, right inferior phrenic, and right renal arteries were selectively catheterized for angiography. If the angiogram showed that the HCC blood supply originated from different vessels, an indwelling microcatheter was inserted in the main feeding artery for HAIC, while the other feeding vessels were embolized without chemotherapeutic drugs. The FOLFOX-based regimen of hepatic-artery perfusion chemotherapy employed doses of oxaliplatin, 85 mg/m^2; calcium folinate, 200 mg/m^2; and 5-fluorouracil, 2.5 g/m^2 of body surface area every 3 weeks. During the study period, dose modifications and treatment interruptions were initiated according to drug-related toxicity grades and the patient's physiological condition (Supplementary Document). In the absence of disease progression, HAIC was performed for four to six cycles, before the patients received angiogenesis inhibitors and PD-1/PD-L1 blockers to consolidate the therapeutic effects over the long term.

Small molecule tyrosine kinase inhibitors (a category of angiogenesis inhibitor) such as sorafenib, lenvatinib, apatinib, donafenib, and anrotinib were administered orally, and the dose was determined based on the instructions for the specific drug. Bevacizumab, another type of angiogenesis inhibitor, was administered intravenously (i.v.) every 3 weeks at a dose of 7.5/15 mg/kg body weight. PD-1 blockade, including pembrolizumab, camrelizumab, tislelizumab, and sintilimab, were administered (i.v.) every 3 weeks at a dose of 200 mg. Toripalimab, another PD-1 blocker, was injected through an (i.v.) drip of 240 mg every 3 weeks, following the instructions for the drug. Atezolizumab, a type of PD-L1 blocker, was administered intravenously every 3 weeks at a dose of 1200 mg. During the study period, dose modification of angiogenesis inhibitors was allowed as recommended according to the drug-related toxicity grade and the patient's physiological condition (Supplementary Document). Doses of PD-1/PD-L1 blockade were not modified. Treatment was discontinued if (a) the tumor progressed, (b) the AEs were intolerable, or (c) the patient was unwilling to undergo treatment.

Assessment of clinical outcomes

We followed patients up every 4–8 weeks to assess the treatment response. The radiological response was assessed following Modified Response Evaluation Criteria in Solid Tumors (mRECIST) based on liver dynamic computer tomography or magnetic resonance imaging. Two radiologists with 5 years of clinical experience independently completed the assessments, and a senior radiologist ultimately confirmed the tumor response results. The outcome measures were OS, PFS, ORR, and AEs. OS was defined as the time from the start date of HAIC to death; PFS was defined as the time from the start date of systemic chemotherapy or HAIC to the date of disease progression or death from any cause; ORR was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR); and AEs during treatment were identified based on patient-reported symptoms, examination-based findings, and clinical laboratory test results. We used the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 to classify AEs from any cause by type and severity.

Statistical analysis

All clinical data are expressed as the mean ± standard deviation, median (range), or number (percentage), as appropriate. To compare baseline characteristics, we compared continuous variables using the Student's *t-test* (or the Mann–Whitney test, if appropriate), while categorical variables were compared using the χ^2 test or Fisher's exact test. To account for the different distributions of covariates between the two groups, we performed 1:1 matching by nearest-neighbor matching based on propensity score (PS), using a caliper width of 0.03. Survival rates were calculated using the Kaplan–Meier method and were compared between the two groups using the log-rank test. We employed a univariate Cox regression model to explore potential risk factors associated with survival time based on matched samples. Significant variables in univariate Cox regression models ($P < 0.05$) were included in multivariate Cox regression. We also performed a subgroup analysis of OS between the two groups for the different protocols. All statistical analyses were conducted using R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). A two-sided P-value < 0.05 was considered to indicate statistical significance.

Results

Baseline patient characteristics

Overall, we evaluated 3923 patients with BCLC stage C HCC who underwent HAIC-based therapy for eligibility. Ultimately, 575 cases were included in this study (200 in the SE group; and 375 in the SI group). The comprehensive essential-case profiles prior to PSM are listed in Table 1. The mean age of the included patients was 50.8 ± 11.2 years in the SE group and 50.22 ± 11.2 years in the SI group. The SE and SI groups included 20 (11.8%) and 38 (10.8%) female patients, respectively. All patients were diagnosed with BCLC stage C HCC and ECOG PS < 2. The SI group

Table 1 Patients' baseline characteristics of the patients with BCLC stage C HCC who received triple therapy

Factors	Before PSM			After PSM		
	Sequential($N=200$)	Simultaneous($N=375$)	*P*.value	Sequential($N=182$)	Simultaneous($N=182$)	*P*.value
Age						
Mean (SD)	50.8 (11.8)	50.2 (10.8)	0.616	51.1 (11.7)	50.7 (10.6)	0.75
Median [Min, Max]	51.0 [21.0, 82.0]	51.0 [23.0, 78.0]		52.0 [21.0, 82.0]	52.0 [26.0, 75.0]	
Sex						
Female	20 (10.0%)	38 (10.1%)	1	18 (9.9%)	17 (9.3%)	1
Male	180 (90.0%)	337 (89.9%)		164 (90.1%)	165 (90.7%)	
HAIC circles						
> 4	176 (88.0%)	141 (37.6%)	< 0.001	160 (87.9%)	74 (40.7%)	< 0.001
≤ 4	24 (12.0%)	234 (62.4%)		22 (12.1%)	108 (59.3%)	
ECOG PS						
0–1	200 (100.0%)	375 (100%)	1	182 (100%)	182 (100%)	1
Hepatitis B virus						
Negative	9 (4.5%)	28 (7.5%)	0.229	9 (4.9%)	15 (8.2%)	0.291
Positive	191 (95.5%)	347 (92.5%)		173 (95.1%)	167 (91.8%)	
Child–Pugh						
A	181 (90.5%)	347 (92.5%)	0.492	165 (90.7%)	172 (94.5%)	0.23
B	19 (9.5%)	28 (7.5%)		17 (9.3%)	10 (5.5%)	
AFP > 400 ng/mL						
No	69 (34.5%)	144 (38.4%)	0.406	61 (33.5%)	70 (38.5%)	0.382
Yes	131 (65.5%)	231 (61.6%)		121 (66.5%)	112 (61.5%)	
Maximum tumor diameter						
Mean (SD)	10.8 (3.66)	10.7 (4.10)	0.707	10.8 (3.67)	10.5 (3.87)	0.558
Median [Min, Max]	10.9 [4.50, 24.0]	10.7 [1.90, 23.5]		10.8 [4.50, 24.0]	10.6 [2.90, 21.5]	
Tumor number						
Single	88 (44.0%)	125 (33.3%)	0.015	74 (40.7%)	78 (42.9%)	0.75
Multiple	112 (56.0%)	250 (66.7%)		108 (59.3%)	104 (57.1%)	
Vascular invasion						
No	34 (17.0%)	82 (21.9%)	0.202	30 (16.5%)	34 (18.7%)	0.68
Yes	166 (83.0%)	293 (78.1%)		152 (83.5%)	148 (81.3%)	
Extrahepatic metastasis						
No	93 (46.5%)	176 (46.9%)	0.991	85 (46.7%)	91 (50.0%)	0.6
Yes	107 (53.5%)	199 (53.1%)		97 (53.3%)	91 (50.0%)	
BCLC						
C	200 (100%)	375 (100%)	1	182 (100%)	182 (100%)	1

BCLC, barcelona clinic liver cancer; HCC, hepatocellular carcinoma; PSM, propensity score matching; HAIC, hepatic arterial infusion chemotherapy; ECOG PS, eastern cooperative oncology group performance status; AFP, alpha-fetoprotein

had more patients with multiple liver lesions ($P=0.015$). The average patient received HAIC 4.50 ± 1.61 times, with patients in the SI group tending to undergo more HAIC sessions (4.76 ± 1.77 *vs.* 4.01 ± 1.10; $P<0.001$). The two groups were comparable in other demographic, clinical, and tumor characteristics ($P>0.05$).

We conducted 1:1 PSM based on age, sex, maximum tumor diameter, number of tumors, and presence of vascular invasion and extrahepatic metastasis (EHM). Age and sex have been verified as significant factors influencing tumor patients' prognosis, especially for the immunotherapy response [26]. Except for sex and age, the factors included in PSM have been used to evaluate the stage in BCLC, China Liver Cancer staging (CNLC), and American Joint Committee on Cancer (AJCC) TNM staging guidelines [4, 27, 28]. After PSM, 182 patients remained in each group, with most features equivalent across both groups ($P>0.05$; Table 2). The median age of the participants was 52.0 years in both groups. In the SI group, 90.7% of patients were male, compared to 90.1% in the SE group. The mean maximum tumor diameter was > 10 cm in both groups. The SE and SI groups included 152 (83.5%) and 148 (81.3%) patients with vascular

Table 2 Tumor response in both groups according to mRECIST after PSM

	Sequential	Simultaneous
CR	0(0%)	17(4%)
PR	74(42%)	190(51%)
SD	84(37%)	120(32%)
PD	42(21%)	48(13%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

invasion, and 97 (53.3%) and 91 (50.0%) with EHM, respectively. The mean number of HAIC sessions was higher in the SI group than in the SE group after PSM (4.68 ± 1.82 *vs.* 3.99 ± 1.11; $P < 0.001$).

Efficacy

The median follow-up time for patients was 10.75 months in the SE group and 14.3 months in the SI group. In PSM-adjusted Kaplan–Meier analyses, the median OS was significantly longer in the SI group than in the SE group (SI: 28.8 months; 95% confidence interval [CI]: 19.3–not reached *vs.* SE: 16.1 months; 95% CI 14.1–25.8; $P = 0.002$; Fig. 2b). The survival rates in the SI and SE groups were 92.2% *versus* 80.8% at 6 months, 72.1% *versus* 62.3% at 12 months, and 53.9% *versus* 42.1% at 24 months, respectively. We also observed significant differences in the median PFS (SI: 9.8 months; 95% CI 8.2–13.4 *vs.* SE: 7.2 months; 95% CI 6.0–9.5; $P = 0.01$; Fig. 2d). The tumor response, assessed in line with mRECIST, is shown in Table 3. After PSM, SI treatment yielded a better response, with a significant difference observed between the two groups (SI *vs.* SE, 58% *vs.* 37%; $P < 0.001$). Notably, 11 patients were evaluated as achieving a CR in the SI group, whereas no patient in the SE group achieved a CR.

The SI protocol (hazard ratio [HR]: 0.61; 95% CI 0.44–0.84), Child–Pugh grade B (HR: 2.39; 95% CI 1.61–3.55), alpha-fetoprotein (AFP) > 400 ng/mL (HR: 1.40; 95% CI 1.07–1.83), larger maximum tumor diameter (HR: 1.04; 95% CI 1.00–1.07), multiple foci (HR: 1.64; 95% CI 1.26–2.15), and EHM (HR: 1.46; 95% CI 1.14–1.88) were identified as possible factors for OS in univariate Cox regression (Fig. 3a). In multivariate Cox regression, SI treatment

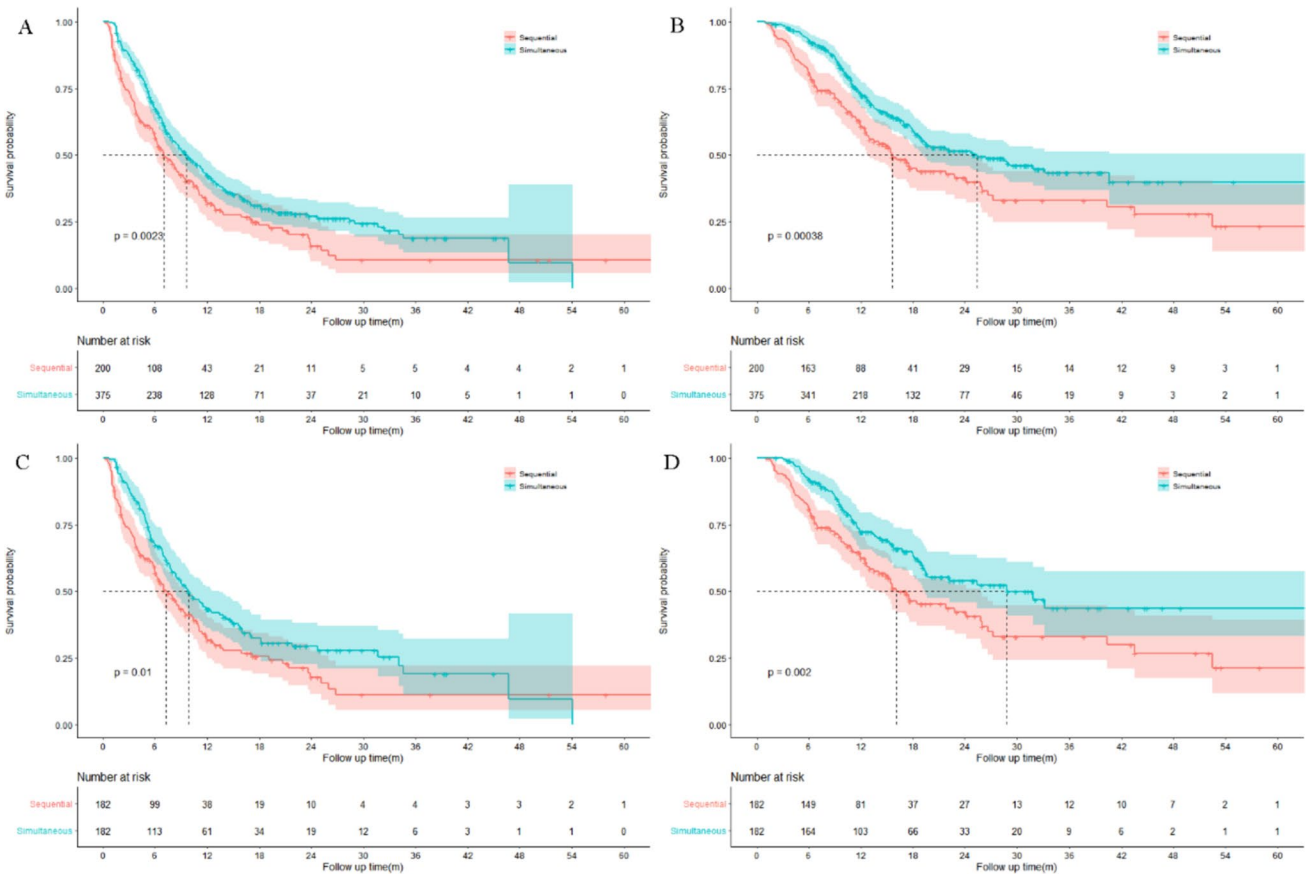

Fig. 2 As determined by Kaplan–Meier analyses, comparisons of progression-free survival **A** before or **B** after PSM and overall survival **C** before or **D** after PSM between the two groups. PSM, propensity score matching

Table 3 Complications comparison related to sequential or simultaneous group after PSM

n (%)	Sequential($N=182$)			Simultaneous($N=182$)		
	Grade1-2	Grade3-4	Total	Grade1-2	Grade3-4	Total
Fever	21 (11.5%)	2 (1.1%)	23 (12.6%)	32 (17.6%)	5 (2.7%)	37 (20.3%)
Nausea	28 (15.4%)	0	28 (15.4%)	56 (30.8%)	0	56 (30.8%)
Vomit	44 (24.2%)	4 (2.2%)	48 (26.4%)	42 (23.1%)	6 (3.3%)	48 (26.4%)
Abdominal pain	79 (43.4%)	13 (7.1%)	92 (50.5%)	100 (54.9%)	19 (10.4%)	119 (65.3%)
Elevated ALT	55 (30.2%)	29 (15.9%)	84 (46.1%)	72 (39.6%)	47 (25.8%)	119 (65.4%)
Elevated AST	61 (33.5%)	35 (19.2%)	96 (52.7%)	76 (41.8%)	42 (23.1%)	118 (64.9%)
Hyperbilirubinemia	48 (26.4%)	18 (9.9%)	66 (36.3%)	80 (44.0%)	17 (9.3%)	97 (53.3%)
Anemia	21 (11.5%)	4 (2.2%)	25 (13.7%)	63 (34.6%)	12 (6.6%)	75 (41.2%)
Neutropenia	57 (31.3%)	13 (7.1%)	70 (38.4%)	59 (32.4%)	41 (22.5%)	100 (54.9%)
Thrombocytopenia	66 (36.3%)	23 (12.6%)	89 (48.9%)	62 (34.1%)	50 (27.5%)	112 (61.6%)
Bleeding	6 (3.3%)	4 (2.2%)	10 (5.5%)	11 (6.0%)	8 (4.4%)	19 (10.4%)
Diarrhea	60 (33.0%)	5 (2.7%)	65 (35.7%)	54 (29.7%)	6 (3.3%)	60 (33.0%)
Hoarseness	33 (18.1%)	0	33 (18.1%)	53 (29.1%)	0	53 (29.1%)
Rash	24 (13.2%)	6 (3.3%)	30 (16.5%)	42 (23.1%)	16 (8.8%)	58 (31.9%)
HFS	34 (18.7%)	21 (11.5%)	55 (30.2%)	49 (26.9%)	21 (11.5%)	70 (38.4%)
Hypertension	39 (21.4%)	24 (13.2%)	63 (34.6%)	37 (20.3%)	27 (14.8%)	64 (35.1%)
RCCEP	52 (28.6%)	6 (3.3%)	58 (31.9%)	60 (33.0%)	8 (4.4%)	68 (37.4%)
Hypothyroidism	37 (20.3%)	0	37 (20.3%)	25 (13.7%)	0	25 (13.8%)
Fatigue	24 (13.2%)	7 (3.8%)	31 (17.0%)	50 (27.5%)	12 (6.6%)	62 (34.1%)
Hepatitis	0	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	1 (0.5%)
Pneumonia	0	0	0	0	1 (0.5%)	1 (0.5%)
Proteinuria	63 (34.6%)	13 (7.1%)	76 (41.7%)	59 (32.4%)	14 (7.7%)	73 (40.1%)
Hepatic encephalopathy	0	0	0	0	1 (0.5%)	1 (0.5%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFS, hand–foot syndrome; RCCEP, reactive cutaneous capillary endothelial proliferation

was associated with lower mortality than SE treatment (HR: 0.64; 95% CI 0.47–0.88; Fig. 3b). Child–Pugh grade B (HR: 1.84; 95% CI 1.07–3.16), AFP > 400 ng/mL (HR: 1.58; 95% CI 1.09–2.27), number of tumors (HR: 1.50; 95% CI 1.07–2.10) and EHM (HR: 1.71; 95% CI 1.23–2.39) were independent factors for OS. In subgroup Cox analysis, the SI group showed a lower HR than the SE group for OS, especially in patients who were male, < 60 years old, with a serum AFP level < 400 ng/mL, Child–Pugh class A, a single tumor, vascular invasion, and/or with EHM (Fig. 4).

Safety

The results showed that the incidence of AEs was significantly higher in the SI group than in the SE group (165/182 [90.6%] *vs.* 144/182 [79.1%]; $P < 0.001$). The most common AE in both groups was abdominal pain, with incidences of 50.5% (92/182) for the SI group and 65.3% (119/182) for the SE group (Table 3). When starting HAIC, most patients (SI *vs.* SE, 119/182 *vs.* 92/182) suffered varying degrees of abdominal pain, especially during the infusion of oxaliplatin. This was typically managed by slowing the speed of infusion or administering anisodamine or lidocaine. The incidence of grade 3–4 AEs was higher in the SI group than in the SE group (128/182 [70.3%] *vs.* 111/182 [60.9%]; $P < 0.001$). In both groups, the incidence of liver dysfunction, including elevation in aspartate aminotransferase levels (SE, 35/182 [19.2%]; SI, 42/182 [23.1%]) or alanine aminotransferase levels (SE, 35/182 [19.2%]; SI, 47/182 [25.8%]) were the most common grade 3–4 AEs, while no grade 5 AEs were reported in either group.

Discussion

Combination treatment for HCC has proven to be a promising strategy; however, how best to perform it remains in question. Many studies that have focused on combination therapy for other cancers have been conducted using the SE or SI method [21–25]. For advanced non-small-cell lung cancer, most studies have shown that SE chemoradiation cannot provide patients with longer-term benefits than concurrent chemoradiation [29, 30]. Based on the current literature and the results of our previous studies [31, 32], we propose that SI triple therapy will prolong survival of patients with uHCC. To the best of our knowledge, this is

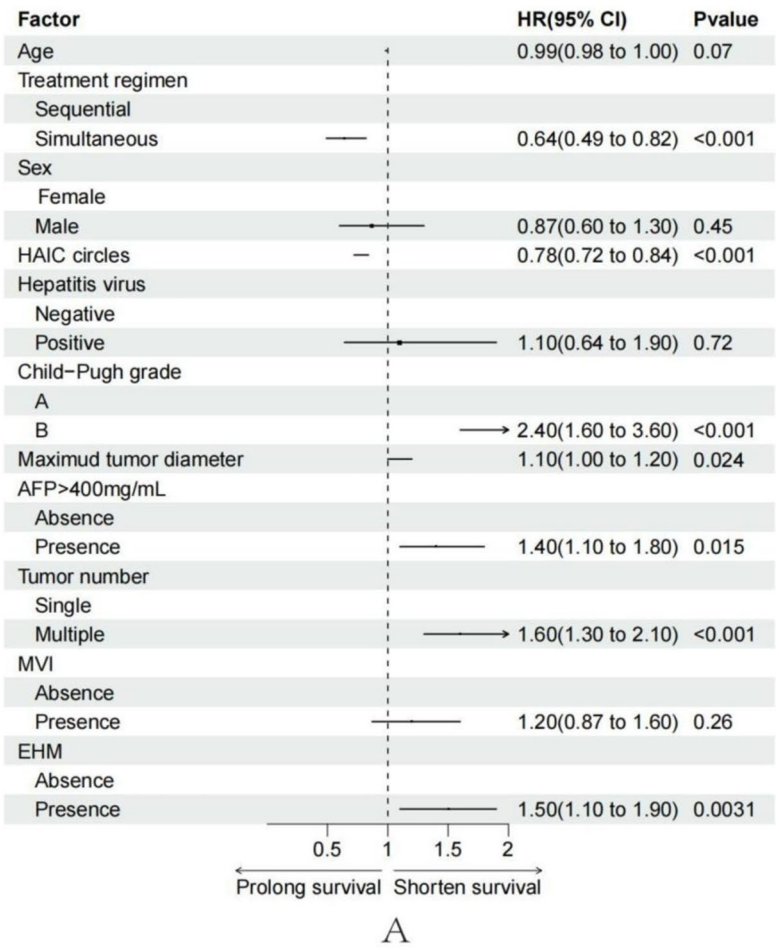

Fig. 3 Cox regression analyses of overall survival: (A) univariate and (B) multivariate. HAIC, hepatic arterial infusion chemotherapy; AFP, alpha-fetoprotein; MVI, macrovascular invasion; and EHM, extrahepatic metastasis

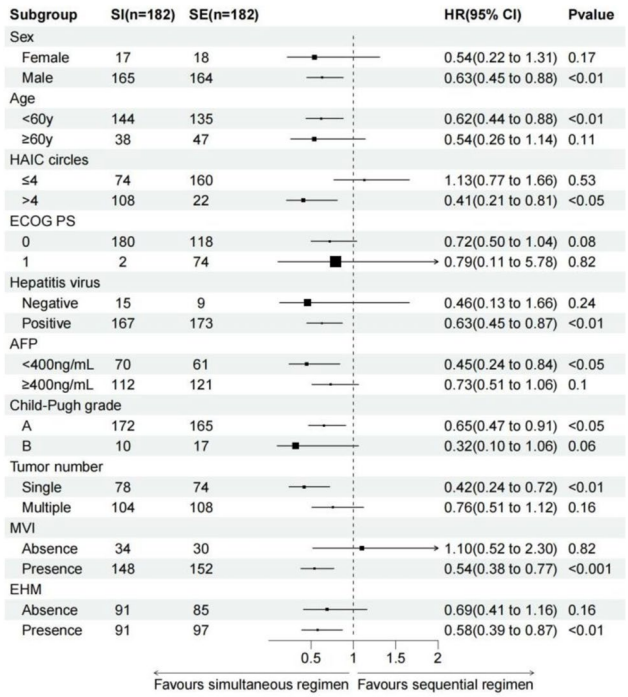

Fig. 4 Subgroup analyses of overall survival for the sequential and simultaneous protocols. HAIC, hepatic arterial infusion chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; MVI, macrovascular invasion; and EHM, extrahepatic metastasis

the first multicenter study to compare the survival rates and safety of triple therapy delivered sequentially *versus* simultaneously. The results showed that SI HAIC combined with systematic therapy was associated with a longer OS and PFS and a higher ORR than its SE counterpart. Univariate and multivariate analyses revealed SI to be an independent predictor of better survival outcomes, while subgroup survival analysis also demonstrated that SI triple therapy was more effective than its SE counterpart. Besides, some patients in the SI group attained a CR, while none did in the SE group; this suggests that an SI regimen might be able to shrink tumors faster and achieve deeper remission.

HAIC controls tumors by killing tumor cells and destroying feeding arteries with high-concentration drugs, leading to the release of tumor-related antigens and switching the tumor from "cold" to "hot." Simultaneous use of ICIs, as represented by PD-(L)1 blockade, can help convert the tumor microenvironment from immunosuppressed to activated, especially in "hot tumors" [33–35]. In addition, the use of anti-angiogenic drugs can prevent tumor angiogenesis, which usually occurs after tumor cell necrosis due to the increased expression of vascular endothelial growth factors [36]. Some studies have investigated the relationship between active angiogenesis and poor prognosis in solid tumors [37, 38], and vascular normalization is thought to help enhance the efficacy of chemotherapy and ICIs [39–41]. Therefore, the concurrent combination of HAIC, anti-angiogenesis, and ICIs is expected to improve the tumor response [42, 43]. Conversely, if the interval between HAIC and systematic therapy is too long, immune cells recruited in the tumor might be exhausted through various pathways and new tumor-feeding microvessels might have been generated [44–50], impairing the efficacy of therapy. Simultaneous treatment can induce tumor necrosis or shrink tumors rapidly, reducing the tumor burden in the liver and further prolonging patient survival. Our results suggested that the earlier the concurrent combination of HAIC and systemic therapy is applied, the better the synergistic effect.

Combination with systematic treatment has already become the first-line treatment for aHCC, and many related regimens have been recommended by several authoritative guidelines. Some studies have revealed that additional use of local therapy such as HAIC can improve prognosis in aHCC [17, 18, 31, 51]. In our study, the ORR (87% per mRECIST), PFS (9.6 months), and OS (25.4 months) of SI triple therapy outperformed those of most anti-angiogenesis–targeted therapies plus PD-(L)1 blockade regimens, such as atezolizumab + bevacizumab (ORR, 33.2% per mRECIST; PFS, 6.9 months; OS, 19.2 months) in the IMbrave150 trial, pembrolizumab + lenvatinib (ORR, 40.8% per mRECIST; PFS, 8.2 months; OS, 21.2 months) in the LEAP002 trial, and camrelizumab + rivoceranib (ORR, 33.1% per mRECIST; PFS, 5.6 months; OS, 22.1 months) in the CARES 310 study [52–54]. Notably, patients in our cohort were diagnosed with heavier tumor burdens than those in most previous studies. Still, the ORR of the SI group was much higher than those of combined systemic therapy groups in other studies, highlighting the importance of HAIC in controlling the tumor burden in aHCC.

Based on the results of previous studies [12, 31], the number of HAIC cycles per patient in our study was four to six, and the HAIC will be discontinued when tumors were found to have progressed. In the first stage, HAIC combined with angiogenesis inhibitors and immune therapy showed a higher ORR than HAIC alone; therefore, more patients were able to receive HAIC continuously. As a result, the SI group experienced more HAIC cycles than the SE group, whether before PSM (4.76 ± 1.77 *vs.* 4.01 ± 1.10; $P < 0.001$) or after (4.68 ± 1.82 *vs.* 3.99 ± 1.11; $P < 0.001$). We also performed subgroup analysis for OS. The results indicated that the SI protocol showed better tumor control in populations with single tumors, vascular invasion, or EHM, meaning that SI local treatment could synergize with systemic treatment regardless of the presence of intra- or extrahepatic lesions. In other words, the SI regimen is more suitable than the SE regimen for aHCC.

Overall, the incidences of AEs were higher in the SI group than in the SE group and in groups receiving targeted

therapy combined with PD-(L)1 blockade in other studies, but were roughly the same as those of groups receiving triple therapy in other studies [15, 16, 19, 20]. Abnormal liver function was a relatively common AE in the SI group, but the effects of HAIC on liver function appeared to be short term, with apparently limited influence on long-term survival. Another common AE in both groups was thrombocytopenia, resulting from not only myelosuppression due to chemotherapy, but also hypersplenism secondary to liver cirrhosis. Thrombocytopenia is usually treated with termination of chemotherapy and platelet booster therapy, followed by splenic arterial embolization or splenic resection; most patients recover after such treatments. Overall, the AEs of triple therapy, whether SE or SI, were controllable and acceptable.

Generally, the simultaneous use of combination therapy showed better efficacy and acceptable safety for aHCC than the sequential use, especially for patients with aHCC who are < 60 years, male, Child–Pugh grade A, AFP < 400 ng/mL, secondary to hepatitis virus, diagnosed with extrahepatic metastasis or vascular invasion. Thus, the simultaneous protocol is recommended first. The above findings reveal that timely simultaneous treatment when the liver function is still reasonable can significantly reduce the intrahepatic tumor load. Effective hepatic tumor reduction could improve prognosis even in cases presenting with extrahepatic metastasis.

This study has several major limitations. First, the study design was retrospective, which might cause selection bias. Second, the kinds of anti-angiogenic drugs and the use of PD-(L)1 differed between groups and individuals. Third, although we included hundreds of patients from different centers, most patients had histories of hepatitis B virus infection. Moreover, the median follow-up period of the study was only approximately 10 months, which limits the value of the study. Consequently, future prospective studies employing larger, multicenter cohorts are required to validate the outcomes.

Conclusion

Simultaneous HAIC plus targeted therapy and PD-(L)1 blockade significantly improved outcomes for patients with BCLC stage C HCC compared to sequential administration of this regimen, with tolerable AEs.

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Author contributions Meng-Xuan Zuo and Chao An participated equally in the study design. Meng-Xuan Zuo, Chao An, Yu-Zhe Cao and Jia-yu Pan made great contribution in the in the data curation, formal analysis, methodology and investigation. Guang-lei Zheng and Jia-Yu Pan have also participated in the study investigation and the data validation. The project administration and supervision were accomplished by An Chao and Meng-Xuan Zuo. Yu-Zhe Cao and Meng-Xuan Zuo had finished the original draft and Meng-Xuan Zuo as well as Chao An has been responsible for the review and editing.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interests The authors declare no competing interests.

Ethical statement All patients were followed up under the hospital ethics committee approval of Sun Yat-sen University Cancer Center (B2023-362–01). The principles of the Declaration of Helsinki were followed.

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