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Sequential vs. concurrent systemic therapies in combination with FOLFOX-HAIC for locally advanced hepatocellular carcinoma: a single-center, real-world cohort study

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Abstract

Background Tri-combination therapy based on hepatic arterial infusion chemotherapy (HAIC) of infusion fluorouracil, leucovorin, and oxaliplatin (FOLFOX-HAIC) plus immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) for the locally advanced hepatocellular carcinoma (HCC) patients have been proven effective. However, whether it was best for these HCC patients to start with the most potent therapeutic pattern was still under debate. This retrospective study evaluated the efficacy and safety of FOLFOX-HAIC combined with systemic therapies in the patterns of sequential and concurrent schedules.

Methods This real-world study included 117 unresectable HCC patients who initially received either FOLFOX-HAIC monotherapy (HAIC group, $n=44$) or concurrent ICIs and TKIs (ConHAIC group, $n=73$) from March 2020 and June 2022, during the period of FOLFOX-HAIC monotherapy in HAIC group, patients in the HAIC group ($n=30$) experienced progressive disease (PD) would have their treatment pattern converted from the FOLFOX-HAIC monotherapy to the combination of FOLFOX-HAIC plus ICIs and TKIs sequentially (SeqHAIC group). The progression-free survival (PFS) and overall survival (OS), as primary outcomes, were compared between patients in the SeqHAIC and ConHAIC groups.

Results The median follow-up time of the SeqHAIC group was 24.92 months (95% CI, 12.74–37.09 months) and of the ConHAIC group was 17.87 months (95% CI, 16.85–18.89 months) and no significant difference was observed in both PFS (HR, 1.572; 95% CI, 0.848–2.916; $p=0.151$) and OS (HR, 1.212; 95% CI, 0.574–2.561; $p=0.614$) between the SeqHAIC and the ConHAIC groups. As for the tumor responses, there was no significant difference between the two groups regarding tumor responses, overall response rates ($p=0.658$) and disease control rates ($p=0.641$) were 50.0%, 45.2%, and 83.3%, 89.0% for the SeqHAIC and the ConHAIC groups, respectively.

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Conclusion Our study revealed that sequential systemic ICIs and TKIs in combination with FOLFOX-HAIC provides similar long-term prognosis and better tolerability compared to concurrent therapy for locally advanced HCC patients. Prospective studies with a larger sample size and longer follow-up are required to validate these findings.

Keywords Hepatocellular carcinoma, Real-world cohort study, Immune checkpoint inhibitors, Tyrosine kinase inhibitors, Hepatic artery infusion chemotherapy

Introduction

Primary liver cancer (PLC) is the third leading cause of cancer mortality worldwide in 2020, of which hepatocellular carcinoma (HCC) accounting for over 70% of PLC cases [1, 2]. Given the insidious onset of HCC, almost 50% of HCC patients in China were diagnosed as locally advanced HCC with macrovascular invasion (MVI) and suffered from a poor median survival of less than 5 months if only received supportive care [3, 4].

Recently, several studies revealed that combination therapies based on the hepatic arterial infusion chemotherapy (HAIC) for borderline resectable or locally advanced HCC had potent effects on the tumor control and conversion rates in the Asia-Pacific region [5–10]. The HAIC of infusion fluorouracil, leucovorin, and oxaliplatin (FOLFOX-HAIC) was able to achieve a 35.4% overall response rate (ORR) for advanced HCC whose ORR was 5.3% if received recommended therapy of sorafenib according to guidelines [8–10]. Moreover, based on HAIC, the ORR could dramatically increase to 54.3-65.9% if concurrently applied chemoradiotherapy or systemic therapies for the locally advanced HCC patients [11–13]. These results raised the interest of clinical practitioners to further explore the efficacy and safety of HAIC-based combination therapies.

Interestingly, our previous study found that FOLFOX-HAIC possessed the ability to enhance the efficacy of following lenvatinib plus programmed death receptor-1 (PD-1) inhibitors in treating HCC patients with portal vein tumor thrombosis (PVTT) [14], which indirectly indicated the timing of combination therapy could play a role in the treatment of HCC patient to some extent. However, whether the sequential combination therapy sacrificed the chance of tumor response for patients who received FOLFOX-HAIC monotherapy initially was still unknown yet. Moreover, due to the sequential and concurrent therapeutic patterns that have been discussed in other malignant tumors [15–17], it also inspired us to investigate these two therapeutic patterns in the treatment of borderline resectable or locally advanced HCC patients which was yet to be discussed in HCC. This retrospective study evaluated FOLFOX-HAIC combined with systemic therapies in the patterns of sequential and concurrent schedules and thus discussed this topic from the perspective of efficacy and safety.

Methods

Patients

The medical records of borderline resectable or locally advanced HCC patients from the Department of Liver Surgery in Sun Yat-sen University Cancer Center (SYSUCC) who initially received FOLFOX-HAIC monotherapy or combination of FOLFOX-HAIC plus immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) at the same course between March 2020 and June 2022 were retrospectively retrieved in this study. The inclusion criteria were: [1] patients were diagnosed with HCC according to clinical or pathological characteristics based on the American Association for the Study of Liver Diseases (AASLD) practice guidelines [18]; [2] borderline resectable or locally advanced HCC and unable to achieve R0 resection initially [19] defined as: (a) a solitary tumor with excessive volume; (b) tumor close contacted with the main vessel; (c) unilobar multifocal disease (either with > 3 tumors or one tumor > 3 cm) or bilobar disease; (d) high-risk of post-hepatectomy liver failure [3]. at least one measurable intra-hepatic lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria; [4] initially received either FOLFOX-HAIC monotherapy (HAIC group) or FOLFOX-HAIC plus ICIs and TKIs at the same course (ConHAIC group); and [5] at least received 1–2 courses of FOLFOX-HAIC. Exclusion criteria were [1] extrahepatic metastasis [2] coexistence of other malignancies or immune-related diseases; and [3] incomplete follow-up data. The protocol complied with the ethical guidelines of the Declaration of Helsinki of the World Medical Association and was approved by the ethics committee of the Sun Yat-sen University Cancer Center (SYSUCC) (approval No. B2022-301-01). All patients provided written informed consent for HCC treatment and the use of their medical records for research purposes.

Treatments

For patients in the HAIC group, FOLFOX-HAIC was performed every 3–4 weeks, chemotherapy agents were infused through a percutaneous microcatheter inserted and placed in the tumor feeding artery identified by repeat arteriography at each course. The following regimen was administered via hepatic artery, oxaliplatin 130 mg/m^2 infusion for 2 h, D1; leucovorin 200 mg/m^2 infusion for 1 h, D1; 5-fluorouracil 400 mg/m^2 infusion bolus followed by 2400 mg/m^2 over 24 h [10]. During the period

of FOLFOX-HAIC treatment, part of patients ($n=30$) detected progressive disease (PD) would have their treatment pattern converted from the FOLFOX-HAIC monotherapy to the combination of FOLFOX-HAIC plus ICIs and TKIs (SeqHAIC group) until convert to surgery, developed PD or intolerable toxicity. For patients in the ConHAIC group, FOLFOX-HAIC procedure was the same as that of the HAIC group. Meanwhile, patients received combined therapy of ICIs and TKIs on the first course of FOLFOX-HAIC until convert to surgery, developed PD or intolerable toxicity. TKIs were administrated on the first day of FOLFOX-HAIC and ICIs were intravenously injected on the second day after the FOLFOX-HAIC was completed. Due to the lack of solid evidence to prove the superiority among various ICIs, the choices of ICIs were mainly based on the patients' medical insurance and economic condition. The TKIs were administrated according to the guidelines (20–21). The exact types and statistical analysis of ICIs and TKIs were listed in the Tables S1 and there was no difference between the SeqHAIC group and the ConHAIC group ($p>0.050$).

Clinical endpoints

The primary clinical endpoints were progression-free survival (PFS) and overall survival (OS). For patients in ConHAIC group, the PFS was defined as the date of treatment initiation to the verified radiological progression during treatment course. For patients in SeqHAIC group, the PFS was defined as date of treatment initiation of FOLFOX-HAIC monotherapy to the verified radiological progression after sequential ICIs and TKIs systemic therapies during treatment course. The OS for both groups was defined as the date of the initiation of FOLFOX-HAIC to the date of death due to any cause. Tumor response to treatment was defined as complete response (CR), partial response (PR), stable disease (SD), or PD based on the RECIST v1.1 criteria [22]. The secondary outcomes included conversion rate, overall response rate (ORR), disease control rate (DCR), and safety. Treatment-related adverse events (TRAEs) were documented during each phase of treatment and assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0) [23].

Evaluation

All baseline data were retrieved from medical records and imaging examinations. All patients generally underwent scheduled blood test, enhanced computed tomography (CT) or magnetic resonance imaging (MRI) every 2–3 months to evaluate the efficacy and safety during the treatment. During the first 2 years of follow-up, complete blood counts, blood chemistry, tumor biomarkers and CT or MRI were repeated every 3 months. Thereafter, patients were examined every 6 months until discovered disease progression or died.

Statistical analysis

Continuous variables were analyzed by using an unpaired student's *t*-test or *Mann-Whitney* test. Categorical variables were compared using the χ^2 or Fisher's exact test. Survival analysis was performed and compared using the Kaplan-Meier method and *log-rank* tests. COX regression was applied to identify the independent risk factors for PFS and OS. Univariate regression was first performed, and all variables were included in the multivariate analysis using the forward conditional method. Moreover, subgroup analysis was conducted based on the different tumor characteristics which might impact on tumor progression or survival on the basis of clinical experience of enrolled patients. All statistical analyses were performed using SPSS (version 25.0; SPSS, Inc., Chicago, United States) or R (version 4.2.1; R Foundation, Vienna, Austria). A two-sided p value <0.050 was considered statistically significant.

Results

Demographic characteristics of the study population

The patient inclusion flowchart was presented in Fig. 1. From March 2020 and June 2022, 117 borderline resectable or locally advanced HCC patients who initially received either FOLFOX-HAIC monotherapy ($n=44$), or concurrent of ICIs and TKIs ($n=73$) were included, during the treatment procession 30 HCC patients converted to SeqHAIC group because of detected disease progression. The baseline characteristics of the HAIC group and the ConHAIC group were presented in the Table S2. The median cycles of FOLFOX-HAIC from initial treatment were 4 [4, 6] in HAIC group and there was no statistic difference in terms of tumor burden between the two groups ($p>0.050$). In general, the cohort included 107 (91.5%) males and 10 (8.5%) females, with an average age of 55.7 years old, most of enrolled patients were hepatitis B virus (HBV) related HCC (100 cases, 85.5%) with preserved liver function. The mean measurable tumor diameter of the enrolled patients was 10.1 cm, and more than half of them suffered from PVTT (71 cases, 60.7%). In addition, as presented in the Table 1, the median cycles of FOLFOX-HAIC from initial treatment were 5 [4, 6] in SeqHAIC group and 4 [3, 4] in ConHAIC group ($p>0.050$), and no significant difference was observed in the other baseline variables of the SeqHAIC group and the ConHAIC group.

Progression-free and overall survival

As of September 1st, 2023, for the overall population, the median follow-up was 18.9 months (95% confidence interval [95% CI], 17.54–20.26 months). As shown in the

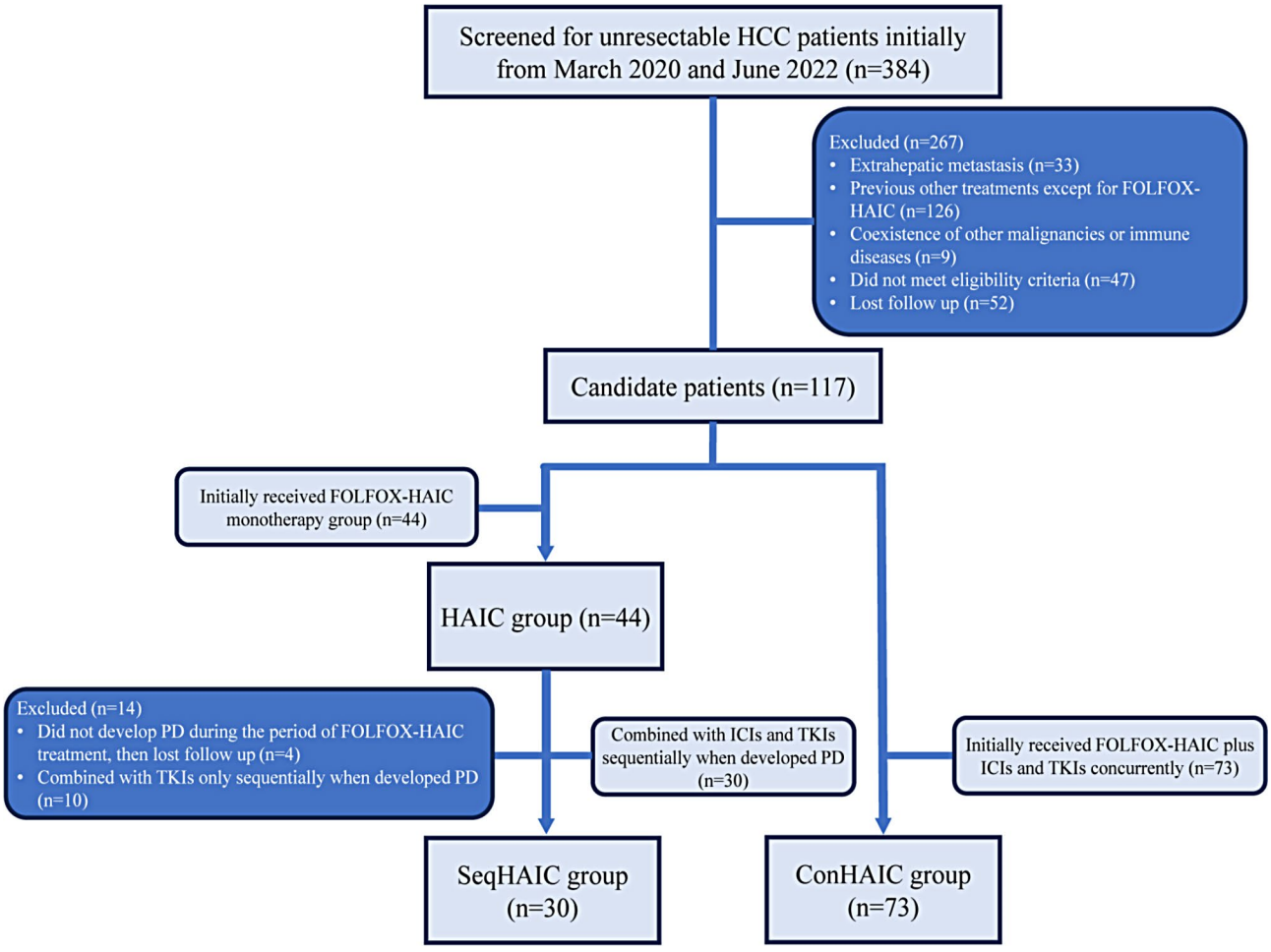

Fig. 1 Patient disposition. HCC, hepatocellular carcinoma; FOLFOX-HAIC, HAIC of infusion fluorouracil, leucovorin, and oxaliplatin; ICIs, immune checkpoint inhibitors; TKIs, tyrosine kinase inhibitors; PD, progressive disease

Fig.S1, the median PFS for all patients was 5.8 months (95% CI, 3.21–8.39 months), and a total of 43 (36.8%) deaths were observed, the median OS was 27.33 months (95% CI, 21.64–33.02 months). The HAIC group demonstrated obvious disadvantage in both PFS (hazard ratio [HR], 10.821; 95% CI, 5.914–19.800; $p<0.001$) and OS (HR, 2.119; 95% CI, 1.137–3.950; $p=0.018$) compared to the ConHAIC group (Fig.S2A-B). For the 44 patients who initiated with the FOLFOX-HAIC monotherapy (HAIC group), only 4 patients did not develop PD, 10 patients combined with TKIs only sequentially when developed PD during the follow-up period. After excluded 14 patients who did not meet eligibility criteria, the rest 30 patients were finally included into the SeqHAIC group for further analysis. Notably, no significant difference was observed in both PFS (HR, 1.572; 95% CI, 0.848–2.916; $p=0.151$) and OS (HR, 1.212; 95% CI, 0.574–2.561; $p=0.614$) between the SeqHAIC and the ConHAIC groups (Fig. 2A-B). In detail, the median follow-up time of the SeqHAIC group was 24.92 months (95% CI, 12.74–37.09 months) and of the ConHAIC group was 17.87 months (95% CI, 16.85–18.89 months). At the data cut-off, 13 (43.3%) and 18 (24.7%) patients died in the SeqHAIC and ConHAIC groups, respectively. The median PFS was 11.6 months (95% CI, 9.34–13.87 months) in the SeqHAIC group and 19.37 months (95% CI, 12.90–25.84 months) in the ConHAIC group, respectively (Fig. 2A). Additionally, the 6-, 12-, 18- and 24-month PFS rates were 83.3%, 40.0%, 16.7% and 3.3%, respectively, in the SeqHAIC group and 53.4%, 37.0%, 13.7% and 2.7% in the ConHAIC group, respectively (Fig. 2A). A total of 25 patients in the ConHAIC group who developed PD or unacceptable toxicity during the follow-up period, appropriate second-line treatments were recommended according to the multi-discipline team (MDT). In detail, 6 patients switched to second-line TKIs monotherapy, 15 patients received combined therapy of ICIs and TKIs, and 4 patients lost follow-up. The median OS of the SeqHAIC group was 27.33 months (95% CI, 18.60-36.06 months), and the median OS of the ConHAIC group was not reached at the data cut-off (Fig. 2B). The 6-, 12-, 18- and 24-month OS rates were

Table 1 Clinicopathological characteristics of patients by different treatment groups

Characteristics	Total (*n* = 103)	SeqHAIC group (*n* = 30)	ConHAIC group (*n* = 73)	*p* value
Age, years, Mean ± SD	55.6 ± 11.7	52.8 ± 13.3	56.8 ± 10.8	0.110
Male, n (%)	95 (92.2)	28 (93.3)	67 (91.8)	1.000
ECOG status, n (%)				0.976
PS = 0	38 (36.9)	11 (36.7)	27 (37.0)	
PS = 1–2	65 (63.1)	19 (63.3)	46 (63.0)	
Child-Pugh score, n (%)				0.789
5	89 (86.4)	25 (83.3)	64 (87.7)	
6	14 (13.6)	5 (16.7)	9 (12.3)	
Tumor size, cm, Mean ± SD	10.0 ± 3.1	10.5 ± 3.2	9.9 ± 3.0	0.542
≥ 10 cm	57 (55.3)	18 (60.0)	39 (53.4)	
< 10 cm	46 (44.7)	12 (40.0)	34 (46.6)	
Tumor number, n (%)				0.324
Single	42 (40.8)	10 (33.3)	32 (43.8)	
Multiple	61 (59.2)	20 (66.7)	41 (56.2)	
PVTT, n (%)				0.053
Yes	63 (61.2)	14 (46.7)	49 (67.1)	
No	40 (38.8)	16 (53.3)	24 (32.9)	
AFP, n (%)				0.764
≥ 400ng/ml	56 (54.4)	17 (56.7)	39 (53.4)	
< 400ng/ml	47 (45.6)	13 (43.3)	34 (46.6)	
PIVKA-II, n (%)				0.316
≥ 1000mAU/ml	85 (82.5)	23 (76.7)	62 (84.9)	
< 1000mAU/ml	18 (17.5)	7 (23.3)	11 (15.1)	
BCLC Stage, n (%)				0.069
A	14 (13.6)	5 (16.7)	9 (12.3)	
B	24 (23.3)	11 (36.7)	13 (17.8)	
C	65 (63.1)	14 (46.7)	51 (69.9)	
ALBI grade, n (%)				0.726
I	66 (64.1)	20 (66.7)	46 (63.0)	
II	37 (35.9)	10 (33.3)	27 (37.0)	
ALT, IU/L, (Median, IQR)	39.4 (29.5, 55.9)	33.7 (25.3, 59.8)	41.7 (30.3, 56.1)	0.537
AST, IU/L, (Median, IQR)	55.0 (39.0, 95.5)	56.9 (39.4, 114.1)	53.6 (38.5, 87.4)	0.195
CRP, mg/L, (Median, IQR)	14.1 (2.9, 28.9)	17.8 (4.8, 30.6)	12.8 (2.7, 28.7)	0.569
HBV infection, n(%)				1.000
Yes	88 (85.4)	26 (86.7)	62 (84.9)	
No	15 (14.6)	4 (13.3)	11 (15.1)	
Cycles of FOLFOX-HAIC from initial treatment, (Median, IQR)	4 (3, 5)	5 (4, 6)	4 (3, 4)	< 0.050

ECOG, eastern cooperative oncology group; PS, performance status; SD, standard deviation; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; BCLC, Barcelona Clinic Liver Cancer; ALBI grade, Albumin-Bilirubin grade; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reaction protein; IQR, interquartile range; HBV, Hepatitis B virus

comparable between the two groups, 100%, 73.3%, 53.3% and 36.7%, and 87.7%, 74.0%, 38.4% and 13.7% in the SeqHAIC and ConHAIC groups, respectively (Fig. 2B).

Response and conversion to resection

The tumor responses were presented in the Fig. 3A and the Table S3. There was no significant difference between the two groups regarding tumor responses, the ORRs and DCRs were 50.0%, 45.2%, and 83.3%, 89.0% for the SeqHAIC and the ConHAIC groups, respectively (Fig. 3A; $p > 0.050$). However, for the 44 patients who received the FOLFOX-HAIC monotherapy, the ORR and DCR were 25% and 43.2% before enrolled in the SeqHAIC group, respectively (11 patients achieved PR and no patients achieved CR). The best response for intra-hepatic target lesions according to the RECIST v1.1 criteria was also shown in the Fig. 3B. 2 patients in the SeqHAIC group and 6 patients in the ConHAIC group suffered from extrahepatic metastasis in the case of stable controlling of the intra-hepatic lesions, respectively (6.7% vs. 8.2%, $p = 1.000$ Fig. 3B). In addition, 3 (10.0%) and 9 (12.3%) patients in the SeqHAIC and the ConHAIC groups had received surgical resection, respectively (Fig. 3B). At the data cut-off, 3 and 5 patients in the SeqHAIC and the ConHAIC groups who converted to hepatectomy experienced an intra-hepatic recurrence but all of them remained alive after receiving subsequent therapies.

Subgroup and prognostic analysis

Given patients in the SeqHAIC group tended to suffer from larger tumor size (10.5 cm ± 3.2 vs. 9.9 cm ± 3.0, $p = 0.542$) while patients in the ConHAIC group had more PVTT (46.7% vs. 67.1%, $p = 0.053$; Table 1), hierarchical subgroup analysis in terms of PFS and OS was further conducted (Fig. 4A-B). After stratification, concurrent FOLFOX-HAIC plus ICIs and TKIs was able to postpone tumor progression for unresectable HCC patients with tumor size smaller than 10 cm (HR, 0.25; 95% CI, 0.08–0.78; $p = 0.017$). No significant difference was observed in both PFS and OS across different tumor numbers, PVTT status and alpha-fetoprotein (AFP) levels in either the SeqHAIC or the ConHAIC group ($p > 0.050$; Fig. 4A-B). Additionally, univariate and multivariate COX analysis was presented in Table 2. After the multivariate COX regression analysis, escalated C-reaction protein (CRP) levels (HR, 3.86; 95% CI, 1.71–8.73; $p = 0.001$) for borderline resectable or locally advanced HCC patients were identified as independently risk prognostic factors for PFS (Table 2).

Toxicity events

Overall, no patient died because of TRAEs during the follow-up period and there was no significant difference

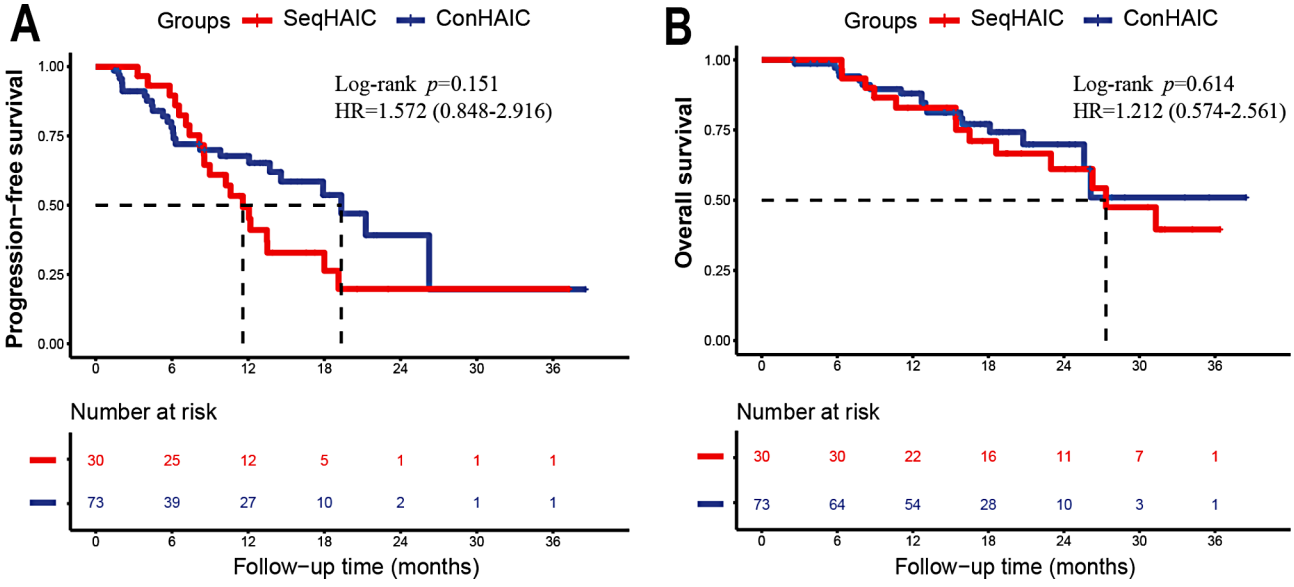

Fig. 2 Kaplan–Meier curves for progression-free survival (**A**) and overall survival (**B**) of patients in the SeqHAIC group ($n=30$) and the ConHAIC group ($n=73$). HR, hazard ratio; CI, confidence interval

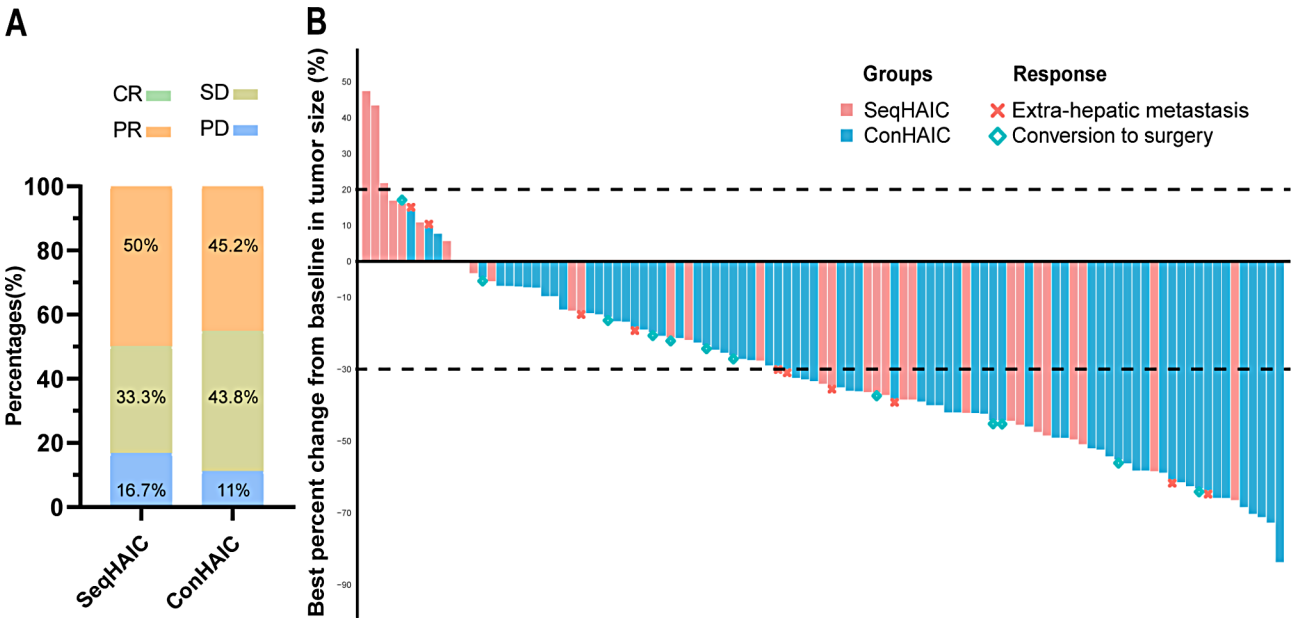

Fig. 3 Barplot for tumor responses rates based on RECIST v1.1 in the SeqHAIC group ($n=30$) and the ConHAIC group ($n=73$) (**A**) and (**B**) Waterfall plot for tumor size changes of intrahepatic target lesions. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

between the SeqHAIC and ConHAIC groups in the types of severe (i.e., grade 3/4) TRAEs (46.7% vs. 61.6%, $p=0.163$; Table 3). The most common TRAEs were albumin decrease (100.0%) and the elevation of total bilirubin (80.6%), while patients in the ConHAIC group underwent significantly more frequent hand-foot-skin reaction (10.0% vs. 28.8%, $p=0.041$) and hypertension (3.3% vs. 21.9%, $p=0.044$) than those of the SeqHAIC group (Table 3).

Discussion

It has been controversial for a long time, whether subject to the most potent therapeutic options directly or gradually for locally advanced HCC patients who were expected to have a chance to receive curative resection theoretically. The present study preliminarily explored the efficacy and safety of these two treatment patterns in treating borderline resectable or locally advanced HCC patients. The results revealed that FOLFOX-HAIC-based sequential or concurrent systemic ICIs and TKIs

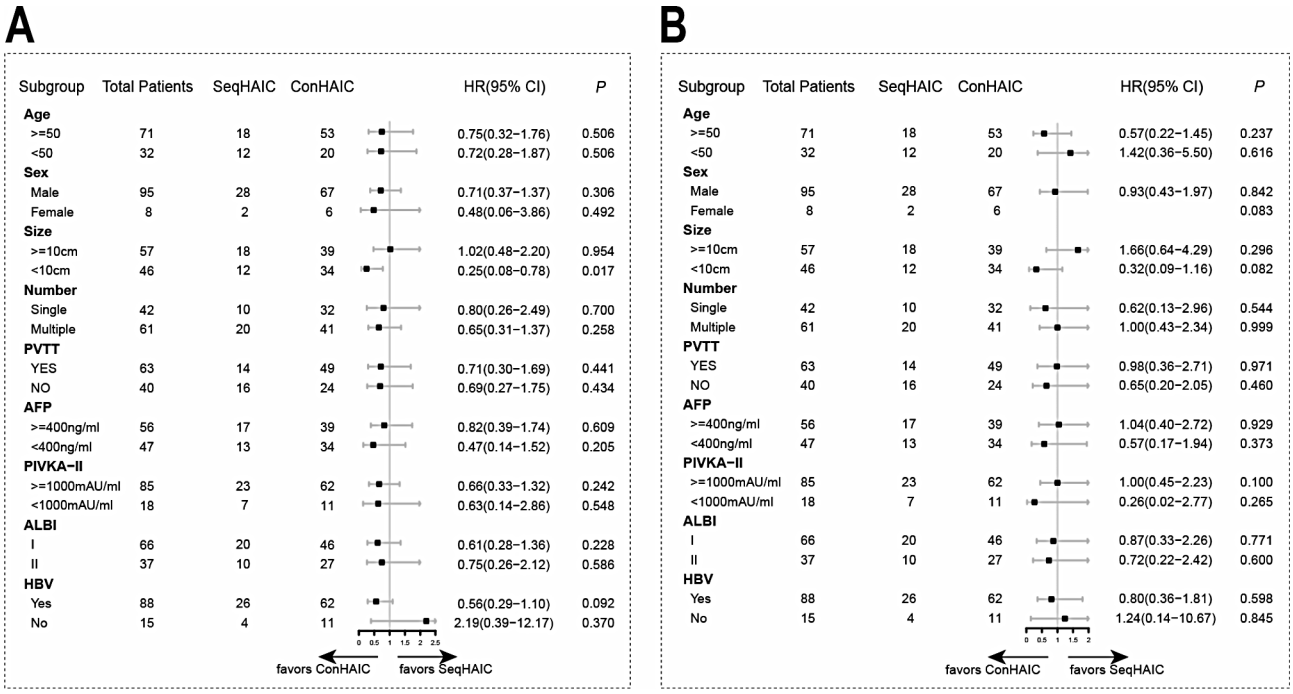

Fig. 4 Forest plots of (**A**) progression-free survival and (**B**) overall survival in terms of interested subgroups for the SeqHAIC and the ConHAIC groups. HR, hazard ratio; CI, confidence interval; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; ALBI, Grade Albumin-Bilirubin grade; HBV, Hepatitis B virus infection

possessed comparable long-term prognosis and tolerability for locally advanced HCC patients, which first provided evidence regarding the timing and sequencing of locoregional and systemic therapies in the treatment of locally advanced HCC patients.

With decades of development across the world, HAIC became a promising locoregional therapy with 27.6-31.5% responsive rates for locally advanced HCC [9, 24, 25]. By placing the catheter to the tumor feeding arterial under digital subtraction angiography (DSA), high concentrations of chemotherapy antigens were able to pump into tumor tissue directly and attenuated the damages towards liver parenchyma [26, 27]. Since Qin et al.. proved the safety and efficacy of FOLFOX4 regimen as systemic therapy for advanced HCC patients [28, 29], the locoregional control rate of HAIC was further improved via applying FOLFOX regimen on HAIC [9]. Li et al.. reported that response rate of FOLFOX-HAIC peaked to 45.9% for large HCC patients who not suitable for resection [7]. Therefore, FOLFOX-HAIC was supposed to be a promising therapy in controlling locally advanced HCC, which has been recommended in some guidelines [6, 21].

Given the potent response rate of FOLFOX-HAIC for locally advanced HCC patients, a series of FOLFOX-HAIC-based combination therapies were carried out by clinical practicians and validated for efficacy. When combined with TKIs, FOLFOX-HAIC plus sorafenib increased 13.7% of DCR compared to FOLFOX-HAIC alone for patients with advanced HCC [30], which preliminarily proved the feasibility of FOLFOX-HAIC-based combinations patterns. Furthermore, as evaluated the HAIC plus ICIs, Wu et al.. revealed that HAIC combined with ICIs had a superior response of PVTT compared to HAIC alone and was correlated to reduced risk of progression or death [31]. Based on the above practice, the FOLFOX-HAIC combined with ICIs and TKIs which was supposed to be the strongest therapeutic patterns for locally advanced HCC patients was reasonable to explore from a multi-center level [32, 33]. The ORRs were able to reach 37–42.5% for FOLFOX-HAIC plus ICIs and TKIs in treatment of intermediate and advanced HCC patients, which was similar to the current study [32, 33]. Therefore, it was believed that FOLFOX-HAIC combined with ICIs and TKIs could be further developed in the future. However, in order to deeply understand the mechanisms behind triple therapy, the roles of locoregional and systemic therapies should be further depicted from different perspectives.

Inspired by Fu et al.. who described the inductive role of FOLFOX-HAIC in treating HCC patients with PVTT with triple therapy [14], the sequence of locoregional and systemic therapies for locally advanced HCC has attracted attention in the clinical practice. The induction therapy of FOLFOX-HAIC and ICIs plus TKIs in the initial period of treatment and then dual maintenance therapy of ICIs and TKIs demonstrated significantly

Table 2 The COX regression analysis for progression free survival and overall survival

Variables	PFS				OS			
	Univariate COX regression		Multivariate COX regression		Univariate COX regression		Multivariate COX regression	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*P* value
Age (50 years)	0.57 (0.32–1.04)	0.067			1.36 (0.62–2.98)	0.439		
Sex (Male)	0.74 (0.26–2.08)	0.566			1.91 (0.26–14.09)	0.527		
Tumor size (≥ 10 cm)	1.43 (0.78–2.59)	0.245			0.90 (0.44–1.86)	0.782		
Tumor number (Multiple)	1.47 (0.78–2.78)	0.234			1.83 (0.81–4.13)	0.146		
PVTT (Yes)	0.71 (0.39–1.29)	0.259			1.02 (0.50–2.12)	0.949		
AFP (≥ 400 ng/ml)	1.65 (0.89–3.07)	0.110			1.22 (0.60–2.48)	0.592		
PIVKA-II (≥ 1000mAU/ml)	1.12 (0.52–2.41)	0.778			1.43 (0.50–4.10)	0.504		
ALT (≥ 50 IU/L)	0.72 (0.37–1.39)	0.328			0.65 (0.28–1.51)	0.312		
AST (≥ 40 IU/L)	0.92 (0.48–1.76)	0.797			1.45 (0.62–3.36)	0.391		
ALBI grade (II)	1.21 (0.67–2.20)	0.534			1.32 (0.65–2.68)	0.443		
HBV infection (Yes)	0.81 (0.34–1.94)	0.634			1.35 (0.47–3.86)	0.579		
CRP (≥ 3 mg/L)	2.44 (1.13–5.26)	0.023	2.60 (1.05–6.45)	0.040	1.02 (0.45–2.29)	0.963		
Underwent SeqHAIC (Yes)	1.54 (0.85–2.77)	0.154			1.21 (0.58–2.51)	0.615		

HR, hazard ratio; CI, confidence interval; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALBI grade, Albumin-Bilirubin grade; HBV, hepatitis B virus; CRP, C-reaction protein

superior disease control rates and long-term prognosis to the systemic therapy alone for HCC patients with PVTT [14]. Oxaliplatin-induced multidrug regimen was reported to induce high levels of necrosis and apoptosis in tumor tissue and release antigens which enhanced the effectiveness of following immune therapy [34, 35]. In the current study, the FOLFOX-HAIC-based combination therapy achieved extremely high ORRs of almost 50%, which obviously higher than systemic combination therapies from other studies for locally advanced HCC patients [36, 37]. Meanwhile, in our clinical practice, as the triplet treatment has a potent efficacy on tumor control, on the other hand, patients also suffer from significantly higher adverse effects. In this study, we compared sequential and concurrent FOLFOX-HAIC plus systemic therapies, and the results indicated that FOLFOX-HAIC sequential ICIs and TKIs did not compromise the efficacy for locally advanced HCC patients, nevertheless, the occurrence of TRAEs was able to significantly decrease which have patients had better compliance and quality of life. In addition, the SeqHAIC group consisted mostly of patients who were resistant to FOLFOX-HAIC monotherapy, but the patients in ConHAIC group were not necessarily refractory to it, which might be the reason of the ConHAIC group seemed to have longer PFS in Kaplan-Meier curve.

Subgroup analysis in the current study revealed that locally advanced HCC patients with tumors less than 10 cm might benefit from FOLFOX-HAIC plus ICIs and TKIs in terms of PFS, while patients with huge tumors failed to demonstrate benefits regardless of sequential or concurrent systemic therapies combined with FOLFOX-HAIC, suggesting that smaller tumors were more likely to be controlled by concurrent FOLFOX-HAIC plus ICIs and TKIs in the short term, but this advantage was not demonstrated in larger tumors. In the multivariate analysis, higher CRP were found to be predictive variables for long-term prognosis, which was similar to other studies [38–40].

With comparable tumor control rate and long-term prognosis, concurrent FOLFOX-HAIC plus ICIs and TKIs significantly increased the incidence of TRAEs. A higher incidence of hand-foot-skin reaction and hypertension was observed in the ConHAIC group, which might be due to direct cytotoxicity to hepatocytes and hematopoietic cells by concurrent FOLFOX-HAIC plus ICIs and TKIs. And the FOLFOX-HAIC sequenced by ICIs and TKIs were able to screen patients who sensitive to FOLFOX-HAIC monotherapy and cloud save money and energies for the subsequent systemic therapies in the future. Moreover, in the ConHAIC group, patients received an average of 3.6 times of FOLFOX-HAIC, while patients in the SeqHAIC group underwent 4.9 times on average, which suggested that the sequential

Table 3 Treatment-related adverse events for the study population

Adverse events	Any grades				Grades 3/4			
	Total (*n* = 103)	SeqHAIC (*n* = 30)	ConHAIC (*n* = 73)	*p* value	Total (*n* = 103)	SeqHAIC (*n* = 30)	ConHAIC (*n* = 73)	*p* value
Treatment-related AEs, n(%)								
Hemoglobin decreased	81 (78.6)	21 (70.0)	60 (82.2)	0.170	3 (2.9)	1 (3.3)	2 (2.7)	0.872
Leukopenia	53 (51.5)	15 (50.0)	38 (52.1)	0.850	3 (2.9)	1 (3.3)	2 (2.7)	0.872
Platelet count decreased	60 (58.3)	16 (53.3)	44 (60.3)	0.516	20 (19.4)	5 (16.7)	15 (20.5)	0.651
ALT increased	52 (50.5)	13 (43.3)	39 (53.4)	0.352	5 (4.9)	1 (3.3)	4 (5.5)	1.000
AST increased	81 (78.6)	23 (76.7)	58 (79.5)	0.754	19 (18.4)	5 (16.7)	14 (19.2)	0.765
Total bilirubin increased	83 (80.6)	25 (83.3)	58 (79.5)	0.651	8 (7.8)	1 (3.3)	7 (9.6)	0.501
Albumin decreased	103 (100.0)	30 (100.0)	73 (100.0)	-	1 (1.0)	0 (0.0)	1 (1.4)	0.405
Creatinine increased	22 (21.4)	4 (13.3)	18 (24.7)	0.203	0 (0.0)	0 (0.0)	0 (0.0)	-
Hypothyroidism	4 (3.9)	1 (3.3)	3 (4.1)	1.000	0 (0.0)	0 (0.0)	0 (0.0)	-
Hand-foot-skin reaction	24 (23.3)	3 (10.0)	21 (28.8)	0.041	0 (0.0)	0 (0.0)	0 (0.0)	-
Pain	15 (14.6)	3 (10.0)	12 (16.4)	0.593	0 (0.0)	0 (0.0)	0 (0.0)	-
Fever	7 (6.8)	1 (3.3)	6 (8.2)	0.642	0 (0.0)	0 (0.0)	0 (0.0)	-
Diarrhea	8 (7.8)	1 (3.3)	7 (9.6)	0.501	0 (0.0)	0 (0.0)	0 (0.0)	-
Fatigue	4 (3.9)	0 (0.0)	4 (5.5)	0.455	0 (0.0)	0 (0.0)	0 (0.0)	-
Nausea	3 (2.9)	0 (0.0)	3 (4.1)	0.147	0 (0.0)	0 (0.0)	0 (0.0)	-
Vomit	5 (4.9)	0 (0.0)	5 (6.8)	0.335	0 (0.0)	0 (0.0)	0 (0.0)	-
Decreased appetite	7 (6.8)	1 (3.3)	6 (8.2)	0.642	0 (0.0)	0 (0.0)	0 (0.0)	-
Edema peripheral	1 (1.0)	0 (0.0)	1 (1.4)	0.405	0 (0.0)	0 (0.0)	0 (0.0)	-
Hypertension	17 (16.5)	1 (3.3)	16 (21.9)	0.044	0 (0.0)	0 (0.0)	0 (0.0)	-

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

strategy enabled the patients to tolerate the side effects of FOLFOX-HAIC better and thus received more treatment courses which were expected to have more durable tumor control. Majority of the TRAEs were generally controllable and did not aggravate the disease, and the abnormal liver function indicators could be recovered between two cycles of HAIC treatment with corresponding supporting medications.

There are potential limitations in the current study. First of all, given the retrospective nature of present study, the selection bias was inevitable. To further discuss this topic, a large-volume and prospective design is needed in the future. Second, in most of population in current study, HBV was the major reason that developed HCC. Whether the survival benefit of different treatment sequencing patterns apply in the absence of HBV has yet to be determined. Finally, in the present study, the types of TKIs and ICIs were comparable between two groups. However, due to the retrospective nature of current study, it was hard to identify the associations between dose of TKIs and the toxicities which we also curious. We hope this question could be answered in prospective in the future.

Conclusion

In conclusion, our study revealed that sequential systemic ICIs and TKIs in combination with FOLFOX-HAIC provides similar long-term prognosis and better tolerability compared to concurrent therapy for locally advanced HCC patients. Prospective studies with a larger sample size and longer follow-up are required to validate these findings.

Supplementary Information

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Supplementary Material 1: **Figure S1** Kaplan–Meier curves for progression-free survival (A) and overall survival (B) of patients in the HAIC and the ConHAIC groups (*n* = 117). Kaplan–Meier curves for progression-free survival (C) and overall survival (D) of patients in the SeqHAIC and the ConHAIC groups (*n* = 103). HR, hazard ratio; CI, confidence interval.

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5: **Figure S2** Kaplan–Meier curves for progression-free survival (A) and overall survival (B) of patients in the HAIC group (*n* = 44) and the ConHAIC group (*n* = 73). HR, hazard ratio; CI, confidence interval

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Author contributions

LS: conceptualization, methodology, software, formal analysis, writing—original draft; ZH: methodology, software, formal analysis; WX: software, data curation, revise; ZY: conceptualization, software, resources, data curation; HZ: resources, investigation; YZ: supervision, data curation; MC: conceptualization, project administration, supervision; DH: resources, funding acquisition, investigation; ZZ: conceptualization, project administration, supervision;

YP: conceptualization, methodology, project administration, supervision, writing—review & editing.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol complied with the ethical guidelines of the Declaration of Helsinki of the World Medical Association and was approved by the ethics committee of the Sun Yat-sen University Cancer Center (SYSUCC) (approval No. B2022-301-01). All patients provided written informed consent for HCC treatment and the use of their medical records for research purposes.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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