Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Combination of Hepatic Arterial Infusion Chemotherapy with Tyrosine Kinase Inhibitor Provides Better Survival in Advanced Hepatocellular Carcinoma Patients

Chung-Wei Liu[1], Po-Ting Lin[2,3], Wei Teng[2,3], Wei-Ting Chen[2,3], Chung-Wei Su[2,3], Yi-Chung Hsieh[2,3], Chen-Chun Lin[3,4], Chun-Yen Lin[2,3], Shi-Ming Lin[2,3]

[1]Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Branch, Tao Yuan City, Taiwan; [2]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, Tao Yuan City, Taiwan; [3]College of Medicine, Chang Gung University, Tao Yuan City, Taiwan; [4]Department of Gastroenterology and Hepatology, New Taipei Municipal Tucheng Hospital, New Taipei City, Taiwan

Correspondence: Po-Ting Lin, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, No. 5, Fu-Hsing Street, Kuei Shan, Tao Yuan City, 333, Taiwan, Tel +886-3-3281200 ext. 8107, Fax +886-3-3272236, Email linpoting0101@gmail.com

Introduction: Hepatic arterial infusion chemotherapy (HAIC) and tyrosine kinase inhibitors (TKI) are widely used to treat unresectable hepatocellular carcinoma (HCC). This study investigated the benefits of combining TKI and HAIC in these patients.

Methods: We retrospectively analyzed patients with unresectable HCC treated at Linkou Chang Gung Memorial Hospital between March 2009 and February 2022. The patients were categorized into two groups: HAIC combined with TKI therapy and HAIC alone. Kaplan–Meier analysis, Cox proportional hazards models, and propensity score matching were applied.

Results: Among 130 patients, the combination therapy group showed significantly improved overall survival (OS) (20.2 versus 11.8 months, $p = 0.000$) and progression-free survival (PFS) (8.2 versus 3.6 months, $p = 0.011$) compared to the HAIC-only group. These advantages persisted after propensity score matching with improved OS (20.2 vs 12.9 months, $p = 0.001$) and extrahepatic PFS (12.4 vs 5.5 months, $p = 0.008$). Combination therapy improved PFS in the stage IV portal vein thrombosis (PVT) subgroup. TKI combination therapy, more than nine HAIC cycles, and post-HAIC transarterial chemoembolization (TACE) were independent predictors of improved OS.

Conclusion: Combining HAIC with TKI therapy improves survival outcomes compared to HAIC alone in patients with unresectable HCC, especially in cases with extrahepatic spread and PVT. Sequential TACE following HAIC therapy further enhances survival benefits.

Keywords: HAIC, TKI, sorafenib, lenvatinib, portal vein thrombosis

Introduction

Liver cancer is the fifth most common type of cancer, accounting for 5.8% of cases worldwide, and it was the third leading cause of cancer-related deaths in 2022, according to the World Health Organization.[1] Hepatocellular carcinoma accounts for 75–85% of all liver cancer.[2] Despite the availability of curative options such as surgical resection and radiofrequency ablation for early hepatocellular carcinoma (HCC), long-term survival rates remain suboptimal.

For patients with unresectable HCC, locoregional therapies such as hepatic arterial infusion chemotherapy (HAIC) or transarterial chemoembolization (TACE) combined with systemic therapy have demonstrated beneficial clinical survival outcomes.[3–8] HAIC has shown potential treatment effects, with median overall survival (OS) rates ranging from 7.1 to 14.9 months and objective response rates (ORR) between 5.1% and 32.0%, especially when using regimens that include cisplatin and 5-fluorouracil (5-FU).[9–15] HAIC is highly regarded because of its ability to minimize systemic toxicity while maximizing the concentration of antitumor agents delivered to the tumor, increasing exposure by as much as 400-

Received: 16 November 2024
Accepted: 7 May 2025
Published: 21 May 2025

fold compared with systemic administration.[16] HAIC is also recommended for patients with HCC in Japan and Taiwan according to the 2023 Taiwan Liver Cancer Association and 2021 Japan Society of Hepatology guidelines.[5,17]

The combination of HAIC with systemic therapy, particularly tyrosine kinase inhibitors (TKI), has expanded treatment options for advanced HCC.[18–21] Although this combination has shown potential, its overall efficacy and safety remain a topic of ongoing discussion. In this real-world study, we assessed the baseline characteristics of patients receiving HAIC and compared survival outcomes between patients treated with HAIC alone and those treated with a combination of HAIC and TKI. Furthermore, we explored the additional survival benefits of sequential treatment following HAIC and TKI therapy.

Materials and Methods

Study Design and Patient Selection

This retrospective cohort study was conducted at a single institution in the Linkou Chang Gung Memorial Hospital. The study was conducted between March 2009 and February 2022. A total of 164 patients who underwent hepatic arterial catheter insertion were identified in our hospital database. The exclusion criteria are demonstrated in Figure 1 and are as follows: (1) age <18 years (2) liver cancer other than HCC (3) coexisting double cancer (4) Barcelona clinic liver cancer (BCLC) stage A (5) HAIC use as adjuvant (6) without image follow-up (7) Post-HAIC liver operation and (8) Child-Pugh scores of class A or B, while excluding those with Child–Pugh class C. All patients were fully reviewed at the institutional HCC Multidisciplinary Conference. Written informed consent was obtained from all study participants before the study began, in accordance with institutional and ethical guidelines set out in the Declaration of Helsinki. This study was approved by the Ethics Committee of the Chang Gung Memorial Hospital (IRB No.: 202002147B0C601).

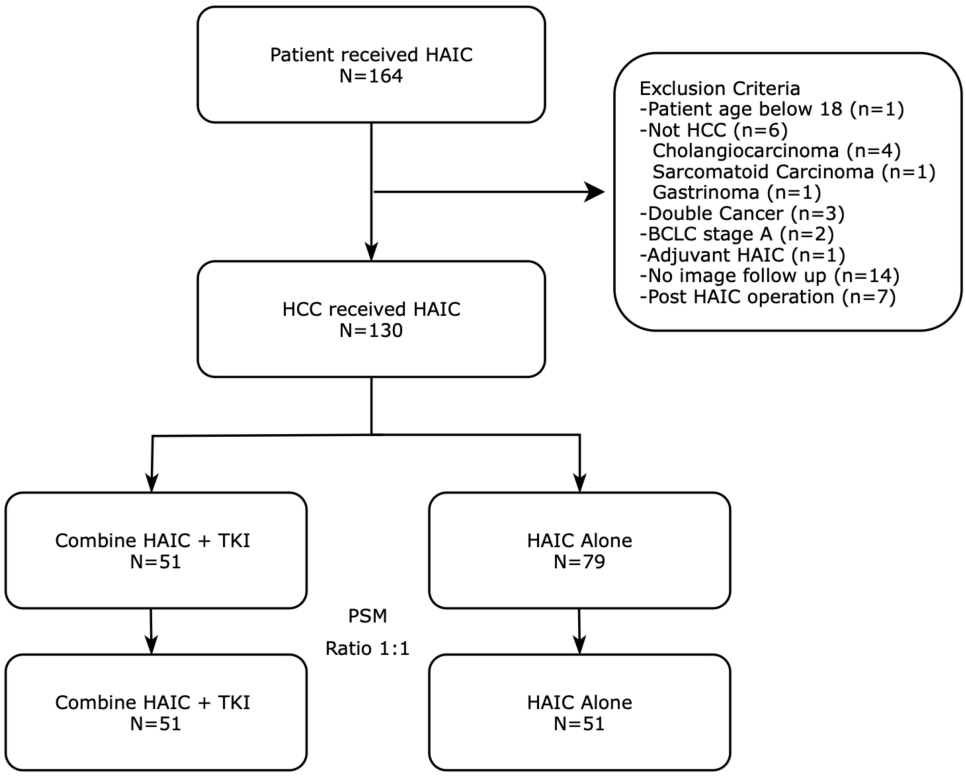

Figure 1 Flow chart of the patient selection.
Abbreviations: HAIC, Hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; TKI, Tyrosine kinase inhibitor; BCLC, Barcelona Clinic Liver Cancer; PSM, propensity score matching.

HAIC Protocol and Systemic Treatment Regimen

The HAIC protocol was the same as that used in a previous study.[22] Each cycle of HAIC consisted of chemotherapy infusion for five days per week, followed by two days of rest. The single course consisted of two consecutive cycles. On the first day of each cycle, proper positioning of the catheter tip was confirmed by fluorescence imaging or radiography. Cisplatin 7 mg/m2 in 100 mL of 0.9% normal saline was infused by pump for 1 h. 5FU 170 mg/m2 mixed with leucovorin 8 mg/m2 in 250 mL of 5% dextrose water was infused by pump over the next 5 h. Oral metoclopramide or ondansetron were used to prevent vomiting. The duration of each cycle was adjusted based on the adverse events.

Sorafenib was administered at a dose of 400 mg orally once daily, with potential escalation to 400 mg twice daily, depending on the patient's tolerance and the severity of adverse events. Lenvatinib was administered orally at 12 mg once daily for patients weighing 60 kg or more or 8 mg once daily for patients weighing less than 60 kg. Regorafenib was administered at 160 mg orally once daily for three weeks, followed by one week of rest in each cycle. Pembrolizumab was administered at 200 mg intravenously every 3 weeks (on day 1 of each 3-week cycle) as it was the only one of our combination immunotherapy treatment. Atezolizumab plus bevacizumab was administered along with atezolizumab at a dose of 1200 mg and bevacizumab at 5–15 mg/kg every 3 weeks. Nivolumab was administered intravenously at 3 mg per kg every 2 weeks. Dose modification was allowed by the attending physicians, depending on the patient's tolerance and severity of adverse events. Adverse effects of systemic treatment were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

Response and Survival Assessment

The HAIC with TKI Combination therapy group was defined as cases in which TKI was administered either during the HAIC course or within three months of HAIC completion.

Treatment response was assessed using the Response Evaluation Criteria in solid tumors 1.1 (RECIST 1.1).[23] Complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD) were also documented. The objective response rate (ORR) was defined as the sum of the CR and PR. Disease control rate (DCR) refers to the sum of CR, PR, and SD.

OS was defined as the period from the start date of the first HAIC therapy until death from any cause, or until the last admission date, or the last outpatient department visit. Progression-free survival (PFS) was defined as the interval from the first HAIC therapy to either radiological disease progression or death episode. Intrahepatic progression was defined as the development of a liver mass or portal vein thrombosis that was limited to liver progression as determined by radiological assessment. By contrast, progression involving locoregional lymph nodes or distant metastases was categorized as extrahepatic progression. Intrahepatic and extrahepatic PFS were defined as the time from the first HAIC therapy to the date of each respective progression event or death. The post-HAIC treatment OS used in supplementary figure S1 was defined as the time from the date of the last HAIC therapy to the same endpoints used for the initial OS definition.

Statistical Analysis

Data for continuous variables are expressed as medians and ranges, and the Mann–Whitney *U*-test was used for comparison. Data for categorical variables were reported as numbers (%), and the chi-square test or Fisher's exact test was used for comparison. Univariate and multivariate Cox proportional hazards models were used for the OS and PFS analyses. Only variables with statistical significance selected in the univariate analyses were included in a multiple regression analysis for OS and PFS. Kaplan–Meier analysis was used to estimate the survival probability between groups, and the Log rank test was used to compare survival outcomes. Statistical significance was set at a two-tailed p-value of <0.05. Statistical analysis was conducted using the SPSS software (version 27; SPSS, Inc., Chicago, IL, USA).

Results

Baseline Characteristics of HCC Patients Receiving HAIC

Our study included 130 hCC patients who met the inclusion and exclusion criteria. The median patient age of total population was 59 years (Table 1). The prevalence of HBV infection was 63.7% in the overall cohort. Among patients

Table 1 Baseline Characteristics of Patients Receiving HAIC Combined with TKI versus HAIC Alone

Variables	All (N=130)	Group		*P* value
		Combine (N=51)	HAIC Alone (N=79)	
Male, n (%)	117 (90)	45 (88.2)	72 (91.1)	0.766
Age (years-old)*	59 (29–79)	59 (36–76)	59 (29–79)	0.977
HTN, n (%)	51 (39.2)	24 (47.1)	27 (34.2)	0.198
DM, n (%)	26 (20)	11 (21.6)	15 (19)	0.823
Alcoholism, n (%)	32 (24.6)	10 (19.6)	22 (27.8)	0.307
HBV/HCV/Both/NBNC, n (%)	51/11/6 (63.7/13.8/7.5)	38/6/3 (74.5/11.8/5.9)	47/14/4 (59.5/17.7/5.1)	0.261
Ascites, n (%)	37 (28.5)	11 (21.6)	26 (32.9)	0.232
Cirrhosis, n (%)	121 (93.1)	49 (96.1)	72 (91.1)	0.481
Child-Pugh score A/B, n (%)	96/34 (73.8/26.2)	44/7 (86.3/13.7)	52/27 (65.8/23.2)	0.014
EV, n (%)	70 (53.8)	24 (47.1)	46 (58.2)	0.280
GV, n (%)	24 (18.5)	11 (21.6)	13 (16.5)	0.494
AJCC stage II/III/IV, n (%)	1/116/13 (0.8/89.2/10)	0/44/7 (0/86.3/13.7)	1/72/6 (1.3/91.1/7.6)	0.388
BCLC stage B/C, n (%)	8/122 (6.2/93.8)	3/48 (5.9/94.1)	5/74 (6.3/93.7)	1.000
Maximum tumor size*	8.8 (1.0–23.4)	8.5 (1.5–20)	8.8 (1–23.4)	0.365
Infiltrative tumor, n (%)	45 (34.6)	17 (33.3)	28 (35.4)	0.852
Up to 7, n (%)	113 (86.9)	43 (84.3)	70 (88.6)	0.596
Up to 11, n (%)	94 (72.3)	35 (68.6)	59 (74.7)	0.548
PVT Nil/I–II/III–IV, n (%)	13/9/108 (10/6.9/83.1)	3/3/45 (5.9/5.9/88.2)	10/6/63 (12.7/7.6/79.7)	0.402
MVI, n (%)	117 (90)	48 (94.1)	69 (97.3)	0.247
Extrahepatic Spread, n (%)	16 (12.3)	7 (13.7)	9 (11.4)	0.786
WBC (10^3/uL)*	5.5 (1.9–14.4)	5.8 (1.9–11.4)	5.4 (1.9–14.4)	0.531
WBC≦4.3k, n (%)	35 (26.9)	15 (29.4)	20 (25.3)	0.687
Hb (g/dL) *	12.2 (7.4–17.2)	12.7 (8.0–17.2)	11.9 (7.4–17.2)	0.144
Platelet (10^3/uL)*	157 (6.5–555)	153 (40–555)	163 (6.5–383)	0.985
INR*	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.2 (0.9–1.5)	0.642
Creatinine (mg/dL)*	0.69 (0.23–2.26)	0.66 (0.35–1.33)	0.72 (0.23–2.26)	0.283
Bilirubin-T (mg/dL) *	0.9 (0.3–4.2)	0.9 (0.3–2.3)	0.9 (0.3–4.2)	0.360
AST (U/L) *	74 (19–537)	73 (19–335)	75 (22–537)	0.219
ALT (U/L)*	51 (11–555)	50 (11–555)	52 (13–300)	0.945
Albumin (g/dL) *	3.59 (2.38–4.80)	3.67 (2.79–4.80)	3.51 (2.38–4.67)	0.091
AFP (ng/mL)*	442 (1–1,968,324)	1006 (3–1,968,324)	262 (1–253,978)	0.077
FIB-4≧3.25_baseline	85 (65.4)	30 (58.8)	55 (69.6)	0.258
FIB-4≧3.25_4 weeks	99 (76.2)	35 (68.6)	64 (81)	0.140
ALBI stage I/II/III_baseline	34/94/2 (26.2/72.3/1.5)	15/36/0 (29.4/70.6/0)	19/58/2 (24.1/73.4/2.5)	0.435
ALBI stage I/II/III_4 weeks	30/92/8 (23.1/70.8/6.2)	12/36/3 (23.5/70.6/5.9)	18/56/5 (22.8/70.9/6.3)	0.991
HAIC cycle	5.5 (2–13)	6 (2–13)	4 (2–13)	0.008
Combine Treatment				
Sorafenib/Lenvatinib/Lenvatinib		42/8/1 (82.4/15.7/2)		
RT, n (%)	90 (69.2)	36 (70.6)	54 (68.4)	0.847
Photon/Proton, n (%)	62/28 (68.9/31.1)	26/10 (72.2/27.8)	36/18 (66.7/33.3)	0.647
RFA, n (%)	8 (6.2)	2 (3.9)	6 (7.6)	0.480
TACE, n (%)	23 (17.7)	11 (21.6)	12 (15.2)	0.358
IO, n (%)	1 (0.8)	1 (2.0)	0	0.392
Post HAIC treatment				
RFA, n (%)	11 (8.5)	6 (11.8)	5 (6.3)	0.339
TACE, n (%)	14 (10.8)	10 (19.6)	4 (5.1)	0.017

(*Continued*)

Table 1 (Continued).

Variables	All (N=130)	Group		*P* value
		Combine (N=51)	HAIC Alone (N=79)	
RT, n (%)	16 (12.3)	9 (17.6)	7 (8.9)	0.174
Chemotherapy, n (%)	14 (10.8)	7 (13.7)	7 (8.9)	0.399
TKI, n (%)	35 (26.9)	9 (17.6)	26 (32.9)	0.069
IO, n (%)	18 (13.8)	11 (21.6)	7 (8.9)	0.066
Follow-up duration (Months)	11.8 (2.2–123.8)	15.5 (2.2–123.8)	6.7 (2.6–102.9)	0.000

Note: * median (range).

Abbreviations: HAIC, Hepatic arterial infusion chemotherapy; TKI, Tyrosine kinase inhibitor; HTN, hypertension; DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; EV, esophageal varices; GV, gastric varices; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; PVT, portal vein thrombosis; MVI, macrovascular invasion; WBC, white blood cell; Hb, hemoglobin; INR, International normalised ratio; Bilirubin-T, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; FIB-4, fibrosis-4; ALBI, albumin-bilirubin score; RT, radiotherapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; IO, immunotherapy.

diagnosed with cirrhosis, the prevalence was 93.1%. Besides 53.8% of the patients exhibited esophageal varices, identified through endoscopy or CT. The median tumor size was 8.8 cm. Most of the cases involve advanced HCC, with a 90% incidence of portal vein thrombosis (PVT) presentation and a 12.3% incidence of extrahepatic spread. Approximately 34.6% of the exhibited infiltrative-type tumors. More than 59% of patients had alpha fetoprotein (AFP) levels >200 ng/mL. On average, patients received 5.5 cycles of HAIC treatment, and 51 patients (39.2%) combined TKI treatment. A higher percentage of patients underwent locoregional treatments such as radiation treatment, TACE, and radiofrequency ablation (RFA) during the course of treatment. After the first cycle of HAIC, fibrosis-4 (FIB-4) and Albumin-Bilirubin (ALBI) scores showed no significant changes from baseline to 4 weeks.

Response and Clinical Outcomes for HCC Patients Undergoing HAIC Treatment

The overall survival of patients receiving HAIC was 15.7 months (95% CI: 12.9–18.6). Progression-free survival was observed to be 5.3 months (95% CI: 1.1–3.1), while intrahepatic PFS was 6.0 months (95% CI: 4.4–7.6), extrahepatic PFS was 8.2 months (95% CI: 6.0–10.3). The best responses in HCC patients treated with HAIC included a partial response in 49 patients (37.7%), stable disease in 23 patients (17.7%), and progressive disease in 58 patients (44.6%). The ORR for all patients was 37.7% and the DCR was 55.4% (Table 2).

Table 2 Efficacy Outcomes of HAIC Combined with TKI versus HAIC Alone

Image Review According to RECIST 1.1	All (N=130)	Combine HAIC+TKI (N=51)	HAIC alone (N=79)	*P* value
Overall survival (months, 95% CI)	15.7 (12.9–18.6)	20.2 (7.9–32.5)	11.8 (8.1–15.6)	0.000
Progression free survival (months, 95% CI)	5.3 (1.1–3.1)	8.2 (6.8–9.5)	3.6 (2.7–4.4)	0.011
Intrahepatic PFS (months, 95% CI)	6.0 (4.4–7.6)	8.4 (6.9–9.9)	4.0 (2.8–5.2)	0.010
Extrahepatic PFS (months, 95% CI)	8.2 (6.0–10.3)	12.4 (8.1–16.6)	5.7 (4.3–7.1)	0.003
Time to progression (months)*	4.0 (0.8–71.4)	7.3 (1.0–67.4)	3.2 (0.8–71.4)	0.023
Best Response				
Partial response, n (%)	49 (37.7)	26 (51.0)	23 (29.1)	0.016
Stable disease, n (%)	23 (17.7)	11 (21.6)	12 (15.2)	0.358
Progressive disease, n (%)	58 (44.6)	14 (27.5)	44 (55.7)	0.002
Objective response rate, n (%)	49 (37.7)	26 (51.0)	23 (29.1)	0.016
Disease control rate, n (%)	72 (55.4)	37 (72.5)	35 (44.3)	0.002

Abbreviations: HAIC, Hepatic arterial infusion chemotherapy; TKI, Tyrosine kinase inhibitor; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; PFS, progression free survival.

https://doi.org/10.2147/JHC.S502922

Additionally, the significant difference between surviving and deceased patients who received HAIC combined with TKI was 52% versus 31.3%, $p = 0.026$ (supplementary table S1).

Predictors of Clinical Outcomes for Survival in HCC Patients Undergoing HAIC Treatment

In univariate analysis (Table 3), the presence of ascites (HR 1.793; 95% CI 1.184–2.716, $p = 0.006$), a higher Child Pugh score (HR 1.658; 95% CI 1.092–2.520, $p = 0.018$), and three or more tumors (HR 1.832; 95% CI 1.247–2.698, $p = 0.002$) were associated with worse progression-free survival. Conversely, a higher number of HAIC cycles (≥9 cycles, HR = 0.326; 95% CI 0.198–0.538, $p<0.001$) and a combination of HAIC with TKI therapy (HR 0.616; 95% CI 0.422–0.900,

Table 3 Cox Regression Analysis for Independent Predictors of Progression Free Survival in Advanced HCC Patients

Variables		Crude HR (95%)	Pvalue	Adjusted HR (95%)	P value
Male	No	Referent			
	Yes	0.673 (0.376–1.207)	0.184		
Age ≥ 70	No	Referent			
	Yes	0.952 (0.497–1.824)	0.881		
HTN	No	Referent			
	Yes	0.703 (0.480–1.029)	0.070		
DM	No	Referent			
	Yes	0.969 (0.612–1.533)	0.892		
Alcoholism	No	Referent			
	Yes	0.960 (0.618–1.490)	0.855		
Ascites	No	Referent			
	Yes	1.793 (1.184–2.716)	0.006		
Cirrhosis	No	Referent			
	Yes	0.586 (0.295–1.165)	0.127		
Child Pugh Score	A	Referent		Referent	
	B	1.658 (1.092–2.520)	0.018	1.341 (0.861–2.091)	0.195
EV	No	Referent			
	Yes	1.012 (0.702–1.460)	0.949		
GV	No	Referent			
	Yes	1.043 (0.653–1.666)	0.861		
BCLC stage	B	Referent			
	C	1.077 (0.500–2.318)	0.850		
AJCC stage	II+III	Referent			
	IV	0.988 (0.515–1.894)	0.970		
HCC max size	< 5cm	Referent			
	≥ 5cm	1.070 (0.691–1.655)	0.763		
HCC number	< 3	Referent		Referent	
	≥ 3	1.834 (1.247–2.698)	0.002	1.654 (1.090–2.510)	0.018
Infiltrative HCC	No	Referent			
	Yes	0.923 (0.627–1.358)	0.684		
Upto7	No	Referent			
	Yes	1.344 (0.780–2.317)	0.287		
Upto11	No	Referent			
	Yes	1.249 (0.834–1.870)	0.280		
PVT	Nil	Referent			
	I+II	0.878 (0.363–2.216)	0.773		
	III+IV	0.787 (0.421–1.473)	0.454		

(*Continued*)

Table 3 (Continued).

Variables		Crude HR (95%)	*P*value	Adjusted HR (95%)	*P* value
MVI	No	Referent			
	Yes	0.794 (0.426–1.482)	0.470		
Extrahepatic spread	No	Referent			
	Yes	1.295 (0.724–2.315)	0.384		
AFP	<1000	Referent			
	≧1000	1.375 (0.946–1.999)	0.095		
ALBI grade	I	Referent			
	II	1.045 (0.690–1.583)	0.836		
	III	2.313 (0.547–9.787)	0.255		
FIB-4	<3.25	Referent			
	≧3.25	1.129 (0.770–1.656)	0.535		
HAIC cycle	2–4	Referent		Referent	
	5–8	0.539 (0.354–0.819)	0.004	0.627 (0.399–0.984)	0.042
	≥9	0.326 (0.198–0.538)	0.000	0.385 (0.227–0.652)	0.000
Combine RFA	No	Referent			
	Yes	1.312 (0.637–2.701)	0.462		
Combine TACE	No	Referent			
	Yes	0.995 (0.623–1.589)	0.983		
Combine RT	No	Referent			
	Yes	0.773 (0.518–1.152)	0.206		
Combine TKI	No	Referent		Referent	
	Yes	0.616 (0.422–0.900)	0.012	0.609 (0.409–0.907)	0.015
Combine IO	No	Referent			
	Yes	1.161 (0.161–8.356)	0.882		
Intrahepatic PD	No	Referent			
	Yes	3.694 (2.189–6.236)	0.000		
Extrahepatic PD	No	Referent			
	Yes	1.697 (1.175–2.451)	0.005		

Abbreviations: HCC, hepatocellular carcinoma; HTN, hypertension; DM, diabetes mellitus; EV, esophageal varices; GV, gastric varices; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; PVT, portal vein thrombosis; MVI, macrovascular invasion; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin score; FIB-4, fibrosis-4; HAIC, hepatic arterial infusion chemotherapy, RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization;; RT, radiotherapy; TKI, Tyrosine kinase inhibitor: IO, immunotherapy; PD, progression disease.

p = 0.012) were associated with improved progression-free survival. In the multivariate analysis, >9 HAIC cycles, combination of TKI therapy, and three or more tumors were independent predictive factors for progression-free survival. This is highlighted by the HAIC ≥9 group, with progression-free survival rates of 15.2 months compared to 3.7 months in the HAIC <9 group, p = 0.001 (supplementary figure S2).

As for overall all survival, the presence of hypertension (HR 0.621; 95% CI 0.390–0.990 p = 0.045), longer HAIC cycles (5–8 cycles HR 0.593 (95% CI: 0.365–0.963) p = 0.035; ≥9 cycles HR: 0.229 (95% CI: 0.119–0.442 p = 0.000), TKI combination therapy (HR 0.439 (95% CI: 0.273–0.706) p = 0.001), and post-HAIC TACE (HR 0.199 (95% CI: 0.072–0.552) p = 0.002) were associated with better survival (supplementary table S2). Additionally, patients who responded to the treatment (ORR (HR 0.173 (95% CI: 0.100–0.302) p = 0.000) and DCR (HR, 0.208 (95% CI: 0.126–0.343) p = 0.000)) were associated with improved overall survival. In contrast, the presence of ascites (HR, 2.390 (95% CI: 1.453–3.931) p = 0.001) and having three or more tumors (HR, 2.127 (95% CI: 1.326–3.411) p = 0.002) were associated with poorer outcomes. In the multivariate analysis, the presence of ascites was the only factor associated with a worse outcome (HR 2.191, 95% CI: 1.268–3.785, p = 0.005). In contrast, receiving more than 9 hAIC cycles (HR 0.249, 95% CI: 0.123–0.504, p = 0.000), TKI combination therapy (HR: 0.492, 95% CI: 0.295–0.822, p = 0.007), and

https://doi.org/10.2147/JHC.S502922

post-HAIC TACE (HR: 0.283, 95% CI: 0.097–0.824, $p = 0.021$) were associated with better outcomes (supplementary table S2).

Comparing the Treatment Efficacy of HCC Patients Receiving HAIC Only Versus HAIC Plus Systemic Treatment

The baseline characteristics of the HAIC with or without TKI groups revealed that the patients receiving combination treatment had a similar composition in terms of age, hepatitis etiology, percentage of cirrhosis, tumor burden, and vascular invasion. However, the combination therapy group had a higher percentage of patients with Child-Pugh stage A (86.3% vs 65.8%, $p = 0.014$). Additionally, more frequent post-TACE treatments were noted following HAIC in the TKI combination group, along with a greater median number of HAIC cycles (six vs four cycles, $p = 0.008$) and a longer follow-up duration (15.5 vs 6.7 months, $p<0.001$) (Table 1). The outcomes of the two groups summarized in Table 2 and Figure 2, which indicate significant differences in survival, including overall survival (20.2 vs 11.8 months, $p = 0.000$), PFS (8.2 vs 3.6 months, p = 0.011), intrahepatic PFS (8.4 vs 4.0 months, $p = 0.010$), and extrahepatic PFS (12.4 vs 5.7 months, $p = 0.003$). Additionally, the objective response rate (51% vs 29.1%, $p = 0.016$) and disease control rate (72.5% vs 44.3%, $p = 0.002$) were also notable in the combination group. In a subgroup analysis of PVT, the combination of HAIC and TKI treatment improved PFS in patients with stage IV (8.4 vs 3.4 months, $p = 0.022$) (supplementary figure S3).

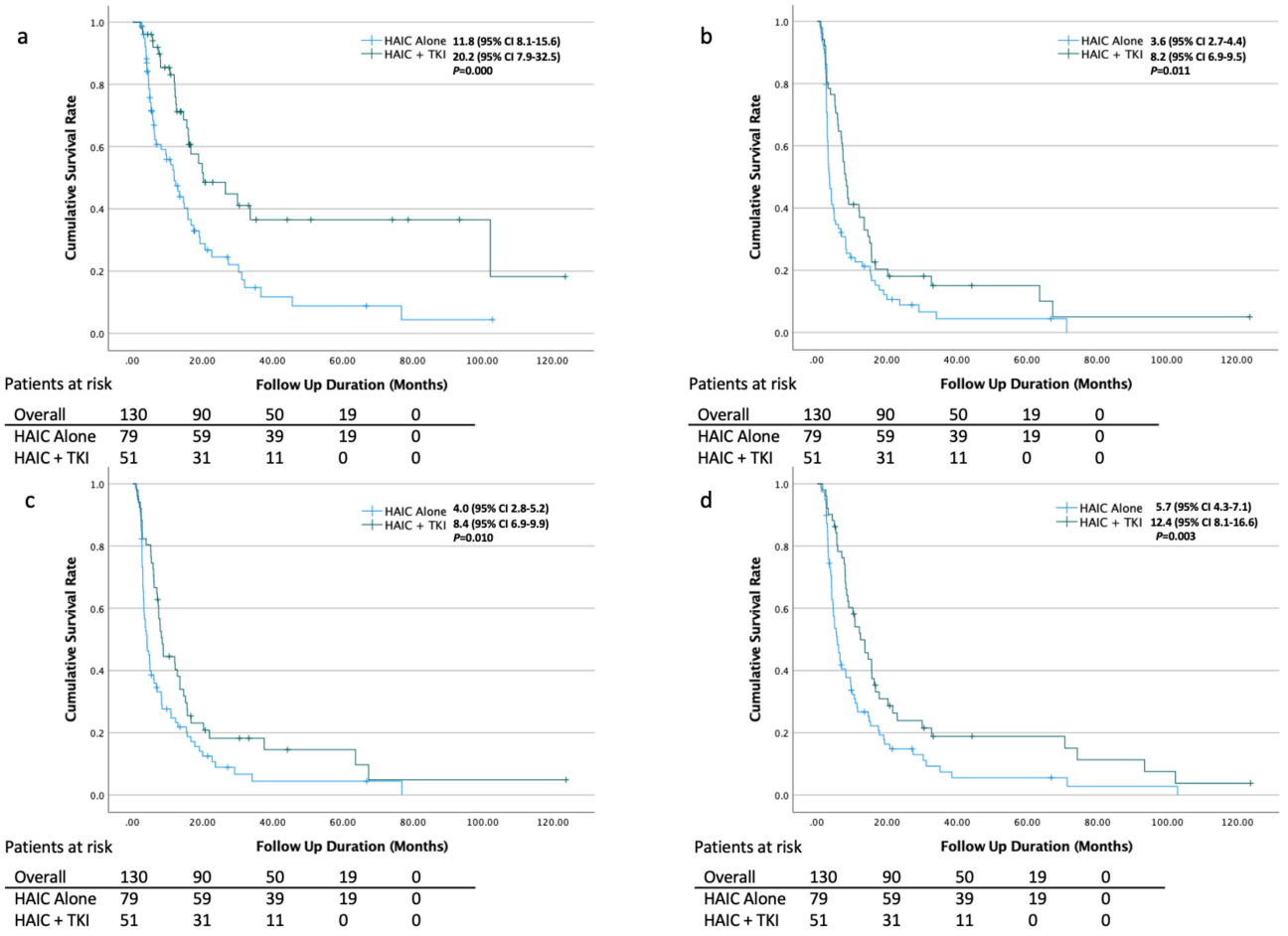

Figure 2 Kaplan–Meier curves of (**a**) overall survival of the entire cohort; (**b**) progression-free survival of the entire cohort; (**c**) intrahepatic progression free survival of the entire cohort; (**d**) extrahepatic progression free survival of the entire cohort.
Abbreviations: HAIC, Hepatic arterial infusion chemotherapy; TKI, Tyrosine kinase inhibitor.

To further identify the effect of the combination treatment, propensity score matching was performed, and 102 patients receiving either HAIC in combination with TKI (n = 51) or HAIC alone (n = 51) were well matched (supplementary table S3 and S4). Outcomes after propensity score match demonstrated significant differences in overall survival (20.2 vs 12.9 months, $p = 0.001$), extrahepatic PFS (12.4 vs 5.5 months, $p = 0.008$), and time to progression (7.3 vs 2.9 months, $p = 0.019$) (supplementary figure S4 and supplementary table S4). However, PFS (8.2 vs 3.3 months, $p = 0.063$) and intrahepatic PFS (8.4 vs 3.7, $p = 0.057$) became not statically significant. Best response showed significant differences in partial response (51% vs 27.5%, $p = 0.025$), progression disease (27.5% vs 54.9%, $p = 0.009$), as well as in ORR (51% vs 27.5%, $p = 0.025$), DCR (72.5 vs 45.1%, $p = 0.009$).

Adverse Effects in HCC Patients Undergoing HAIC

According to the adverse events listed (Table 4), thrombocytopenia (≥ grade 3, 18.5%;, total 66.9%) emerged was the most prevalent, followed by anemia (≥ grade 3, 11.5%;, total 46.9%) and hepatitis (≥ grade 3, 2.3%;, total 30.8%). Gastrointestinal side effects such as nausea (41.5%), vomiting (37.7%), and anorexia (34.6%) were particularly notable Complications related to the Port-A catheter included dermatologic reactions affecting 25 patients (19.2%) and infections

Table 4 Adverse Events for Patients Receiving HAIC with or without TKI

Variables	All (N=130)	Combine (N=51)	HAIC alone (N=79)	*P* value
	CTCAE adverse event grade ≥3/ all grade, n (%)			
Anemia	15/61 (11.5/46.9)	4/23 (7.8/45.1)	11/38 (13.9/48.1)	0.077* 0.857
Thrombocytopenia	24/87 (18.5/66.9)	10/39 (19.6/76.3)	14/48 (17.7/60.8)	0.820* 0.085
Leukopenia	13/33 (10/25.4)	4/15 (7.8/29.4)	9/18 (11.4/22.8)	0.566* 0.416
Hepatitis	3/40 (2.3/30.8)	2/17 (3.9/33.3)	1/23 (1.3/29.1)	0.561* 0.698
Hyperbilirubinemia	2/35 (1.5/26.9)	1/12 (2/23.5)	1/23 (1.3/29.1)	1.000* 0.547
	Event, n (%)			P value
Fever	10 (7.7)	3 (5.9)	7 (8.9)	0.739
Headache	2 (1.5)	1 (2)	1 (1.3)	1.000
Dizziness	6 (4.6)	0	6 (7.6)	0.081
Malaise	13 (10)	4 (7.8)	9 (11.4)	0.566
Hair Loss	2 (1.5)	2 (2.5)	77 (97.5)	0.519
Hiccup	5 (3.8)	3 (5.9)	2 (2.5)	0.380
Fatigue	19 (14.6)	4 (7.8)	15 (19)	0.125
Anorexia	45 (34.6)	19 (37.3)	26 (32.9)	0.706
Nausea	54 (41.5)	21 (41.2)	33 (41.7)	1.000
Vomiting	49 (37.7)	16 (31.4)	33 (41.8)	0.269
Diarrhea	22 (16.9)	8 (15.7)	14 (17.7)	0.815
Constipation	5 (3.8)	2 (3.9)	3 (3.8)	1.000
Abdominal distention	32 (24.6)	12 (23.5)	20 (25.3)	1.000
Abdominal pain	38 (29.2)	17 (33.3)	21 (26.6)	0.435
Port-A infection	13 (10)	5 (9.8)	8 (10.1)	1.000
Port-A dysfunction	3 (2.3)	2 (3.9)	1 (1.3)	0.561
Port-A dermatologic reaction	25 (19.2)	12 (23.5)	13 (16.5)	0.365
Port-A surgical intervention	19 (14.6)	9 (17.6)	10 (12.7)	0.455
Hold HAIC due to side effect	10 (7.7) **	6 (11.8)	4 (5.1)	0.189

Note: **P* value of CTCAE ≥ grade 3, all grade events. ***Hold due to celiac root stenosis related HAIC failure (n=2), HAIC infection (n=1), catheter exposure (n=1), vomiting (n=1), general malaise (n=2), hepatitis (n=1), abdominal pain (n=1), allergy (n=1).

https://doi.org/10.2147/JHC.S502922

at the Port-A site in 13 patients (10%). There was no significant difference in the incidence of side effects between the combination and single HAIC groups. The rate of thrombocytopenia episodes was higher in the combined group; however, this difference was not statistically significant ($p = 0.081$). A few cases of HAIC were discontinued because of various complications, including celiac root stenosis (n = 2), infection (n = 1), catheter exposure (n = 1), vomiting (n = 1), general malaise (n = 2), hepatitis (n = 1), abdominal pain (n = 1), and allergy (n = 1). Complication events of complications did not show a significant difference between the two groups (11.8% vs 5.1%, $p = 0.189$).

Sequential Treatment After HAIC Therapy

Locoregional and systemic therapies were followed by HAIC therapy. Among the total patients, RFA, TACE and radiotherapy (RT) were administered to 8.5%, 10.8%, and 12.3% of the patients, respectively. Additionally, systemic therapies, including chemotherapy, TKI and immunotherapy (IO) were administered to 10.8%, 26.9% and 13.8% of the patients, respectively. Sequential treatment following HAIC showed that TACE benefits on overall OS (HR, 0.283; 95% CI 0.097–0.824, $p = 0.021$) (supplementary table S2). Kaplan–Meier analysis supports the post-HAIC locoregional treatments (LRT) (11.7 vs 5.8 months, $p = 0.006$) (supplementary figure S1A), and supplementary figure S1B highlights the advantage of post-HAIC TACE (100.6 vs 7.4 months, $p = 0.001$). No significant differences were observed in the survival of patients with HCC who received other sequential treatments.

Discussion

This retrospective study demonstrated that HAIC combined with TKI resulted in superior survival outcomes compared to HAIC alone in patients with unresectable HCC without any additional side effects. Furthermore, the combination of HAIC and TKI treatment was particularly effective in cases of extrahepatic spread and PVT4.

Our results highlight that patient in our study achieved significantly better survival rates than those documented in referenced articles comparing cisplatin-based HAIC combined with sorafenib versus sorafenib monotherapy for advanced HCC.[5,6,9,24] First, we used lower and split doses of cisplatin for HAIC. This regimen potentially reduces toxicity while maintaining an effective response and a good performance status. Second, the longer HAIC cycle duration of our regimen appears to contribute to better outcomes than those reported in other studies. Finally, the availability of additional sequential therapy options was associated with an improved overall survival. Systemic treatment or locoregional therapy following HAIC treatment can prolong tumor control and patient survival if liver function is well maintained. The longer duration and higher percentage of sequential treatment may be attributed to the benefits of using a reduced-dose regimen.

In our cohort, we observed improved survival outcomes with the combination of HAIC and TKI, particularly in patients with extrahepatic spread. As expected, TKI provided additional control over extrahepatic spread when used alongside locoregional treatment with HAIC. Moreover, combining TKI not only enhances systemic treatment control but also offers benefits for sequential therapies. Previous studies have shown that TKI can modify the tumor's vascular environment, potentially enhancing the efficacy of subsequent TACE treatments. Among them, sorafenib inhibits the RAF/MEK/ERK pathway, which is commonly upregulated in chemoresistant HCC cells.[25,26] TKIs also acts as an anti-angiogenic agent by inhibiting receptors such as VEGFR and PDGFR, improving the quality of tumor vasculature by reducing vascular permeability and interstitial fluid pressure.[27,28] This enhancement increases the local concentration of agents delivered via HAIC, resulting in a synergistic anticancer effect.[29] This suggests that combining TKI with HAIC not only improves initial treatment outcomes but also optimizes the effectiveness of follow-up locoregional therapies, such as TACE, by changing the local tumor microenvironment. An image of a typical case is presented in Supplementary Figure S5.

In the presence of main portal vein thrombosis (PVT) in HCC, the portal vein blood flow decreases significantly, leading to a reduction in hepatic function. Therefore, the reduction of thrombosis is highly desirable for patients outcome.[11] A randomized control trial in Japan indicates that patients with main portal vein thrombosis IV (PVT4) treated with sorafenib combined with HAIC had a median overall survival of 11.4 months (95% CI 7.0–15.9), compared to 6.5 months (95% CI 4.5–8.4) for those treated with HAIC alone.[30] In our subgroup analysis of PVT4 (supplementary figure S3), we found that combining HAIC with TKI significantly improved PFS rates to 8.4 months (95% CI 6.2–10.6),

compared to 3.4 months (95% CI 2.1–4.6) for HAIC alone ($p = 0.022$). Additionally, other types of PVT or non-PVT HCC did not demonstrate significant outcomes when HAIC was combined with TKI compared with HAIC alone. Therefore, in patients with PVT4, HAIC alone may not be sufficient to control the tumor, and its combination with systemic treatment should be considered.

Liver function plays a crucial role in optimizing clinical outcomes in HCC, bridging this gap with sequential therapy. Our study identified side effects such as thrombocytopenia, liver function impairment, and gastrointestinal symptoms, consistent with the findings of other studies. However, our HAIC regimen differs by utilizing lower daily doses instead of concentrating the dose into a single day, as has been observed in other randomized control trials.[6,9,24,30] This method has been shown to reduce liver damage. Despite the lower daily doses, the total HAIC dosage in our regimen remained adequate for tumor control, as demonstrated by the outcomes discussed earlier. Therefore, separating the HAIC dose in our regimen minimized liver damage and further optimized patient outcomes.

The limitations of our study are multifactorial. First, our data were sourced from a single institution, which may have affected the diversity of our patient population. Second, the retrospective study design may have resulted in the underestimation of side effects due to the study design and recall bias. Third, the use of RECIST 1.1 criteria due to the hepatic vein-related hypodensity of some HCC could limit comparability with other studies. Fourth, the limited number of post-HAIC assessments resulted in a small sample size. Fifth, no interaction analysis was performed to verify the potential synergistic effects between subsequent TACE and more than nine cycles of HAIC, which needs further research of prospective designs or interaction modeling. Finally, the variability in the cohort years from 2009 to 2022 to impact the consistency of management due to the development of pharmaceuticals over the study period.

Conclusion

In our real-world study, HAIC combined with TKI therapy resulted in better survival outcomes than HAIC alone in patients with advanced HCC. Furthermore, HAIC combined with TKI treatment is particularly effective in cases of extrahepatic spread and PVT. Additionally, the sequential use of TACE following HAIC and TKI therapy demonstrates further survival benefits.

Abbreviations

HTN; Hypertension; DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; EV, esophageal varices; GV, gastric varices; AJCC, American Joint Committee on Cancer; BCLC, Barcelona Clinic Liver Cancer; PVT, portal vein thrombosis; MVI, macrovascular invasion; WBC, white blood cell; Hb, hemoglobin; INR, International normalised ratio; bilirubin-T, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; FIB-4, fibrosis-4; ALBI, albumin-bilirubin score; HAIC, Hepatic arterial infusion chemotherapy; TKI, Tyrosine kinase inhibitor; RT, radiotherapy; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; IO, immunotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; CTCAE, Common Terminology Criteria for Adverse Events; RECIST 1.1, Response evaluation criteria in solid tumors 1.1; 5-FU, 5-fluorouracil; PSM, propensity score matching.

Data Sharing Statement

On reasonable request, the data supporting this study can be obtained from the corresponding author.

Ethics Approval and Informed Consent

Written informed consent was obtained from all study participants before the study began, in accordance with institutional and ethical guidelines set out in the Declaration of Helsinki. This study was approved by the Ethics Committee of the Chang Gung Memorial Hospital (IRB No.: 202002147B0C601).

Acknowledgments

The authors thank all members of the Cancer Center, Chang Gung Memorial Hospital, for their invaluable assistance. The authors also appreciate their assistance with data acquisition and cleaning.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Grants from Chang Gung Medical Research Fund (CMRPG3M03- 91 and CMRPG3Q0011), NSTC 112-2314-B-182A-016-MY3, and National Science Council, Taiwan (NMRP- G3N6011).

Disclosure

The authors have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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