Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Clinical Therapy: HAIC Combined with Tyrosine Kinase Inhibitors and Programmed Cell Death Protein-1 Inhibitors versus HAIC Alone for Unresectable Hepatocellular Carcinoma

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Purpose: The majority of new diagnoses of hepatocellular carcinoma (HCC) still pertain to unresectable cases. Currently, the combination therapy of tyrosine kinase inhibitors (TKIs) and programmed cell death protein-1 (PD-1) inhibitors has become the mainstream treatment. According to multiple clinical guidelines, it is strongly advised to consider local therapy as the primary treatment choice for uHCC. This research was conducted to examine the safety and effectiveness of combining hepatic arterial infusion chemotherapy (HAIC) with TKIs and PD-1 inhibitors for the treatment of uHCC.

Methods: Between 2015 and 2020, 208 HCC patients received HAIC alone or HAIC in combination with TKIs and PD-1 inhibitors. The overall survival(OS), and progression-free survival(PFS) and the best treatment response were compared between the two treatment groups. Propensity score matching (PSM)was used to minimize confounding bias.

Results: Among the enrolled patients, 116 patients (55.8%) received combination therapy, while 92 patients (44.2%) received HAIC alone. The baseline characteristics were similar between the two groups. After PSM, 82 pairs of well-matched liver cancer patients were selected; the overall response rate in the combination group trended better than that in the HAIC alone group. The hazard ratios (HRs) for OS and PFS of the combination approach compared to the HAIC-alone approach were 0.47 (95% CI, 0.322–0.687; p<0.001) and 0.58 (95% CI, 0.397–0.848; p=0.005), respectively.

Conclusion: For uHCC patients, combination therapy can provide better OS and PFS compared to HAIC alone.

Keywords: hepatocellular carcinoma, TKIs, PD-1, HAIC, combination therapy

Introduction

Hepatocellular carcinoma (HCC) is a prevalent malignant tumor globally, ranking sixth in terms of occurrence and third in cancer-related mortality. HCC has a poor prognosis, accounting for 8.3% of global cancer deaths by 2020. The survival rate at the five-year mark is only between 11.7% and 14.2%.[1,2]

Sorafenib has emerged as the primary systemic therapy for unresectable HCC, but its longest recorded survival period is merely 6.5 months according to the Oriental trial.[3] Targeted drugs like apatinib and lenvatinib have shown objective response rates (ORR) ranging from 10.7% to 18.8%, yet single targeted therapies are not considered ideal due to their limited efficacy.[4] Immunotherapy drugs such as ramucirumab and tislelizumab offer longer survival

Received: 2 May 2024
Accepted: 25 July 2024
Published: 12 August 2024

periods of approximately 8.5 to 13.2 months respectively. Combining tyrosine kinase inhibitors (TKIs) with PD-1 inhibitors can enhance tumor immune microenvironment reconstruction and synergistically inhibit tumor growth, resulting in improved outcomes compared to monotherapies alone.[5–7] Although some dual drug combinations like camrelizumab plus apatinib, atezolizumab plus bevacizumab, and nivolumab plus ipilimumab have demonstrated certain results, their overall survival periods remain unsatisfactory within the range of 21.8 to 24 months.[8] Despite significant advancements in targeted immunotherapy for liver cancer over recent years, only a small proportion of patients experience lasting clinical benefits.

Both NCCN guidelines and CNLC guidelines recommend transarterial chemoembolization (TACE) as the initial treatment option for primary liver cancer.[9–11] However, Li et al[12] discovered that hepatic artery infusion chemotherapy (HAIC) yielded significantly higher objective response rates (ORR) than TACE group did (46% vs18%, p<0.001). Moreover, the HAIC group exhibited longer median overall survival(mOS)(23.1[95% CI,18 0.5 −27 0.7]months vs 16 0.1[95% CI,14.3 −17 0.9]months, p<0.001). The efficacy of HAIC-FOLFOX as a treatment modality for uHCC has been demonstrated. Previous studies have shown that patients in the HAIC group achieved a significantly longer maximum survival period of approximately 13.9 months compared to around 8.2 months in the sorafenib group (HR 0.408; 95% CI, 0.301–0 0.552; p <0 0.001).[13] As a result, the Chinese Society of Clinical Oncology has suggested considering HAIC-FOLFOX as a viable alternative treatment choice for uHCC.[14]

Yuan[15] previously reported the effectiveness of combining TACE-HAIC targeted immunotherapy with PVTT treatment for uHCC. The combination group exhibited a much higher overall response rate compared to the TACE group, with rates of 53.7% and 7.8%, respectively (p <0.001). Furthermore, the mOS in the combination group demonstrated a significant improvement compared to that in the TACE group (not yet reached versus 10.4 months, p <0.001). However, there is currently no existing literature comparing HAIC combined with targeted immunotherapy versus HAIC alone in liver cancer patients. Hence, the objective of this retrospective analysis is to assess and contrast the rates of overall survival (OS) and progression free survival (PFS) between uHCC patients receiving combination therapy and those undergoing monotherapy with HAIC.

Materials and Methods

Patients

Following the China Liver Cancer (CNLC) guidelines, Hepatic Arterial Infusion Chemotherapy (HAIC) is recommended for patients demonstrating resistance to Transarterial Chemoembolization (TACE) or for those with a diagnosis of locally advanced Hepatocellular Carcinoma (HCC). In China, the FOLFOX regimen is typically utilized either as a sole treatment strategy or in conjunction with systemic therapy. In our study, each case was fully discussed by a multidisciplinary tumor board including interventional radiologists, oncologists and hepatic surgeons. After the discussion, treatment options based on tumors size, number, histologic analysis, and hepatic function were presented to the patient. The treatment decision was finally made jointly by doctors and patients and informed consent was signed by the patient. The research involved a group of 770 individuals diagnosed with unresectable hepatocellular carcinoma (uHCC), and the process for selecting participants is illustrated in Figure 1. A total of 208 uHCC patients were included in this study, out of which 116 received combination therapy while the remaining 92 underwent HAIC alone. The study was approved by the ethics committee of Sun Yat-Sen University. The requirement for informed consent for the present study was waived by the committee due to the retrospective nature of the study. The study was carried out in accordance with the 1964 Declaration of Helsinki and its subsequent amendment.

The eligibility criteria encompassed: (a) HCC patients who initiated treatment with HAIC; (b) Individuals aged between 18 and 75 years old; (c) Those with a Child-Pugh score of either A or B; (d) Eastern Cooperative Oncology Group (ECOG) performance status rated as either 0 or 1; and finally, (e) Patients presenting one or more measurable target lesions. On the other hand, exclusion criteria consisted of: (a) Severe underlying heart, lung, or kidney conditions; (b) History of another primary malignancy diagnosis; (c) Patient refusal to undergo treatment; and lastly, but not least important, (d) Loss to follow-up.

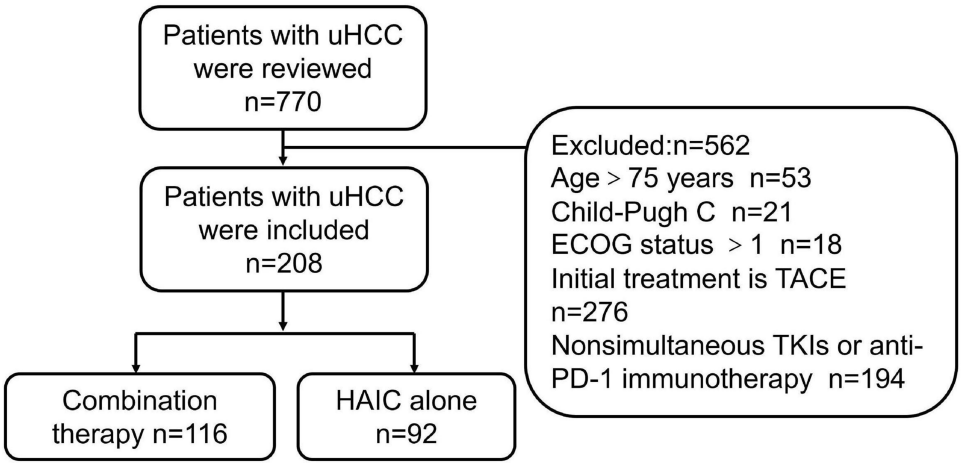

Figure 1 Flow diagram of HCC patients who underwent combination therapy or HAIC.

Treatment

HAIC treatment involved the administration of FOLFOX-based chemotherapy infusion through a catheter placed and secured in the tumor-supplying artery. The dosage included an infusion of oxaliplatin at 85 mg/m^2 for 2 hours, folinic acid at 400 mg/m^2 for 2 hours, and either a 400-mg/m^2 or 2400 mg/m^2 infusion of 5-FU for either 23 or 46 hours.[16–18] At intervals of approximately three to four weeks with a minimum requirement of two sessions per cycle. Transarterial chemoembolization (TACE) was performed for at least one session. Within one week post-surgery and until either disease progression or occurrence of severe treatment-related side effects, patients received targeted kinase inhibitor (TKI) therapy comprising renvastinib, sorafenib, or apatinib. Intravenous administration of programmed cell death protein-1 (PD-1) inhibitors took place either immediately after surgery or within a week thereafter. The PD-1 inhibitors employed in this investigation encompassed toripalimab, camrelizumab, tislelizumab, and sintilimab with an administration frequency ranging from every three to four weeks.

Response Assessment

According to the revised criteria for evaluating response in solid tumors (mRECIST), tumor response encompasses complete response (CR), partial response (PR), disease stabilization (SD), or disease progression (PD). Overall survival (OS) is defined as the duration from initial treatment until death related to cancer. Progression-free survival (PFS) refers to the period starting from the commencement of treatment until either there is advancement of the disease or demise resulting from any reason. The calculation of disease control rate (DCR) involves the summation of CR, PR, and SD. On the other hand, objective response rate (ORR) is determined by summing up CR and PR. Patients underwent imaging every 3–4 weeks for follow-up purposes. Treatment-related adverse events were assessed using version 5.0 of the Common Terminology Criteria for Adverse Events.

Statistical Analysis

In order to mitigate selection bias in both groups, we employed propensity score matching to compare the combination group with the HAIC group. To evaluate continuous variables, we employed either independent or paired sample *t*-tests. For comparing categorical variables, the $\chi 2$ test was utilized. The clinical parameters of the two groups were evaluated using both the Mann–Whitney *U*-test and $\chi 2$ test. Kaplan-Meier curves were utilized to analyze OS and PFS, followed by comparison using logarithmic rank tests. The study investigated the prognostic importance of different factors in predicting survival by conducting both univariate and multivariate regression analyses. All statistical analyses and PSM analyses were conducted utilizing SPSS 24.0 software package, employing bilateral testing with a significance level set at less than 0.05.

Results

Patient Characteristics

In this study, a total of 208 patients were enrolled, with 92 receiving HAIC and 116 undergoing combination therapy. The median follow-up period was 36.4 months (range:1.5–80) for the HAIC group and 15.6 months (range: 6.7–87) for the

combination therapy group. The data in Table 1 showed a statistical difference in AST between the two groups of patients. After propensity matching, the two groups showed similar baseline features.

Tumor Response

The findings of the intervention are displayed in Table 2. In general, the HAIC groups exhibited an ORR of 56.9% and 25.9%, respectively (P<0.001), along with a DCR of 82.8% and 58.3%, respectively (P < 0.001), as per mRESIST

Table 1 Baseline Patient Characteristics

Variable	Before PSM			After PSM		
	Combination therapy (n=116)	HAIC alone (n=92)	*p*	Combination therapy (n=82)	HAIC alone (n=82)	*p*
Gender			0.788			0.786
Male	102 (88.0%)	82 (89.1%)		75 (91.5%)	74 (90.2%)	
Female	14 (12.0%)	10 (11.9%)		7 (8.5%)	8 (9.8%)	
Age			0.841			0.849
≥60	24(20.7%)	18 (19.6%)		18(22.0%)	17 (20.7%)	
<60	92(79.3%)	74 (80.4%)		64(78.0%)	65 (79.3%)	
PLT			0.847			1
≥100	113(97.4%)	90(97.8%)		80(97.6%)	80(97.6%)	
<100	3(2.6%)	2 (2.2%)		2(2.4%)	2 (2.4%)	
ALT			0.435			0.873
≥40	73(62.9%)	53 (57.6%)		49(59.8%)	50 (61.0%)	
<40	43(37.1%)	39 (42.4%)		33(40.2%)	32 (39.0%)	
AST			0.001			0.575
≥40	92(79.3%)	53 (57.6%)		65(79.3%)	62(75.6%)	
<40	24(20.7%)	39 (42.4%)		17(20.7%)	20 (24.4%)	
ALB			0.333			0.23
≥35	101(87.1%)	84 (91.3%)		74(90.2%)	78 (95.1%)	
<35	15(12.9%)	8 (8.7%)		8(9.8%)	4 (4.9%)	
PT			0.09			0.514
≥13.5	16(13.8%)	6 (6.5%)		4(4.9%)	6 (7.3%)	
<13.5	100(86.2%)	86 (93.5%)		78(95.1%)	76 (92.7%)	
TBIL			0.567			0.319
≥17.1	36(31.0%)	32 (34.8%)		24(29.3%)	30 (36.6%)	
<17.1	80(69.0%)	60 (65.2%)		58(70.7%)	52 (63.4%)	
AFP			0.067			1
≥400	65(56.0%)	63 (68.5%)		34(41.5%)	34(41.5%)	
<400	51(44.0%)	29 (31,5%)		48(58.5%)	48(58.5%)	
Maximum tumor diameter			0.151			0.753
≥10	72(62.1%)	48 (52.2%)		45(54.9%)	47 (57.3%)	
<10	44(37.9%)	44 (47.8%)		37(45.1%)	35 (42.7%)	
PVTT			0.353			0.435
Present	53(45.7%)	48 (52.2%)		37(45.1%)	42 (51.2%)	
Absent	63(54.3%)	44 (47.8%)		45(54.9%)	40(48.8%)	
Distant metastasis			0.153			0.863
Present	41(35.3%)	24 (26.1%)		23(28.0%)	24 (29.3%)	
Absent	75(64.7%)	68 (73.9%)		59(72.0%)	58 (70.7%)	
Operation			0.001			0.001
Present	32(27.6%)	5 (5.4%)		28(34.1%)	3(3.7%)	
Absent	84(72.4%)	87 (94.6%)		54(65.9%)	79 (96.3%)	

Note: Statistical significance was assessed with the χ^2 test or the Fisher's exact test.

Abbreviations: PLT, platelet ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; PT, prothrombin time; TBIL, total bilirubin; AFP, alpha-fetoprotein; PVTT, portal vein tumour thrombus; HAIC, hepatic arterial infusion chemotherapy;

Table 2 Treatment Efficacy Evaluated by mRECIST Criteria in the Two Treatment Groups

Variable	Before PSM			After PSM		
	Combination therapy (n=116)	HAIC alone (n=92)	*p*	Combination therapy (n=82)	HAIC alone (n=82)	*p*
Complete response	1(0.8%)	3(3.3%)	0.211	0	2(2.4%)	0.155
Partial response	65(56.0%)	20(21.7%)	<0.001	43(52.4%)	19(23.2%)	<0.001
Stable disease	37(31.9%)	29(31.5%)	0.954	37(45.1%)	29(35.4%)	0.203
Progressive disease	13(11.2%)	37(40.2%)	<0.001	11(13.4%)	36(43.9%)	<0.001
Overall response rate	66(56.9%)	23(25.0%)	<0.001	43(52.4%)	21(25.6%)	<0.001
Disease control rate	100(86.2%)	52(56.5%)	<0.001	71(86.6%)	46(56.1%)	<0.001

Note: Summary of best response. Values are presented as *n* (%). *P* values were calculated using a two-sided χ^2 test.

criteria. Consequently, after PSM, the overall response rates between ORR and DCR were observed to be 52.4% vs 24.4% in the combined and HAIC groups, with a significant difference (P<0.001); similarly, they were determined to be at levels of 86.6% vs57 0.3%, again showing statistical significance (P <0.001).

mOS and mPFS

There was a total of 137 deaths observed during the follow-up period, with 69 deaths (59.5%) occurring in the combination group and 68 deaths (73.9%) in the HAIC group. As shown in Figure 2, Post propensity score matching (PSM), the combination group had 48 deaths (58.5%), while the HAIC group had 62 deaths (75.6%). The mOS was significantly longer in the combination group, with a value of 30.6 months (95% CI: 23.4~37.8), compared to the HAIC group which had a mOS of 15.4 months (95% CI:11.7~19.1) (p<0.001); The combination group demonstrated a significantly longer mPFS of 10.9 months (95% CI: 7.8~14) compared to the HAIC group with a mPFS of 6.4 months (95% CI: 5.6~7.2) (p =0.016). After conducting propensity score matching, the combined group demonstrated a mPFS of 12.1 months (95% CI: 9.3–15), while the HAIC group exhibited an mPFS of 6.0 months (95% CI: 4.7–7.3) (p =0.004). In terms of mOS, the combined group showed a duration of 32.5 months (95% CI: 24.3–40.7), whereas the HAIC group had an mOS of 14.7 months (95% CI: 11.9–17.5) (p<0.001).

The combination group exhibited OS rates of 89.40%, 61.70%, and 41.0% at one, two, and three years respectively, while the HAIC group had rates of 61.30%, 29.50%, and 21.60%. In terms of PFS rates, the combination group showed percentages of 47.60%, 24.80%, and 19.80% at one, two, and three years respectively; whereas the HAIC group had percentages of 27.60%, 21.40%, and 14.60%.

Prognostic Factor Analysis

According to the results presented in Table 3, the cox regression model for univariate analysis revealed that therapy options (combination vs HAIC), AFP levels, presence of PVTT, and occurrence of distant metastasis were found to be significant factors contributing to mortality in overall survival (p<0.05). The multivariate analysis using the cox model revealed that treatment options (hazard ratio [HR]=0.566 [0.398–0.803], p=0.001) and distant metastasis (HR=1.746 [1.216–2.506], p=0.003) were important predictors of overall survival. Similarly, the cox regression model was employed for univariate analysis to identify risk factors associated with mPFS. The results revealed that therapy options, AFP levels, PVTT presence, and distant metastasis were significantly correlated with progression-free survival (p<0.05) (Table 4). In the multivariate analysis using the cox model, treatment options (HR=0.648 [0.457–0.920], p=0.015) and distant metastasis (HR=1.580 [1.099 −2.272], P=0.014) emerged as significant predictors of progression-free survival. The risk factors observed before propensity score matching between the two groups remained consistent after propensity score matching.

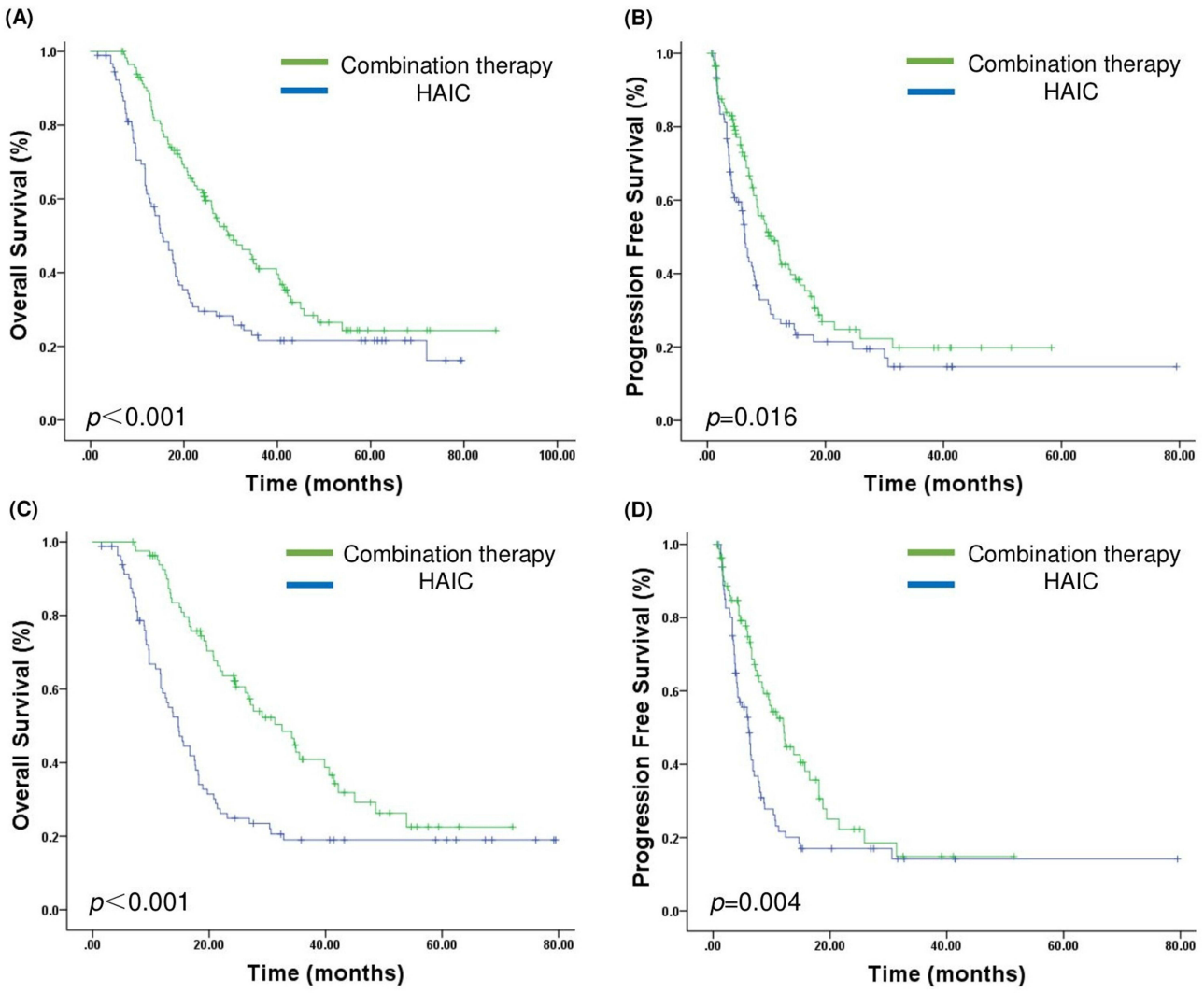

Figure 2 Kaplan–Meier curves of hepatocellular carcinoma (HCC) patients by different therapies in (**A**) overall survival (OS) before matching; (**B**) progression-free survival (PFS) before matching; (**C**) OS after matching; (**D**) PFS after matching.

Treatment Safety

All adverse events observed were of mild intensity and manageable, with no reported fatalities associated with adverse reactions. The most frequently observed adverse reactions in both treatment groups were Elevated ALT/AST (86.2% vs

Table 3 Univariable and multivariable Cox regression analyses for time to OS

Variables	Group	Univariable		Multivariable	
		HR 95%CI	P value	HR 95%CI	P value
Treatment	Combination therapy HAIC	0.549(0.392-0.769)	p<0.001	0.566(0.398-0.803)	p=0.001
Gender	male female	1.035(0.614-1.744)	p=0.897		
Age	≥60 <60	0.751(0.49-1.152)	p=0.19		
PLT (10^9/L)	<100 ≥100	1.363(0.434-4.284)	p=0.596		
ALT(U/L)	>40 ≤40	1.095(0.776-1.544)	p=0.606		

(*Continued*)

Table 3 (Continued).

Variables	Group	Univariable		Multivariable	
		HR 95%CI	P value	HR 95%CI	P value
AST(U/L)	>40	0.982(0.663-1.453)	p=0.926		
	≤40				
ALB(g/L)	<35	0.681(0.419-1.107)	p=0.121		
	≥35				
TBIL(μmol/L)	>17.1	1.239(0.865-1.775)	p=0.243		
	≤17.1				
PT(s)	>13.5	0.653(0.360-1.183)	p=0.160	0.700(0.384-1.276)	p=0.244
	<13.5				
AFP (ng/ml)	>400	1.504(1.057-2.140)	p=0.023	1.300(0.905-1.869)	p=0.156
	≤400				
Main tumor size(cm)	≥10	1.206(0.856-1.699)	p=0.283		
	<10				
PVTT	Present	1.587(1.132-2.224)	p=0.007	1.372(0.971-1.939)	p=0.073
	Absent				
Distant metastasis	Present Absent	1.558(1.093-2.222)	p=0.014	1.746(1.216-2.506)	p=0.003

Table 4 Univariable and multivariable Cox regression analyses for time to PFS

Variables	Group	Univariable		Multivariable	
		HR 95%CI	P value	HR 95%CI	P value
Treatment	Combination therapy	0.664(0.474-0.929)	p=0.017	0.648(0.457-0.920)	p=0.015
	HAIC				
Gender	male	1.269(0.753-2.139)	p=0.372		
	female				
Age	≥60	0.800(0.522-1.227)	p=0.307		
	<60				
PLT (10^9/L)	<100	1.433(0.455-4.511)	p=0.539		
	≥100				
ALT(U/L)	>40	1.026(0.728-1.448)	p=0.882		
	≤40				
AST(U/L)	>40	0.741(0.500-1.098)	p=0.135		
	≤40				
ALB(g/L)	<35	0.779(0.480-1265)	p=0.313		
	≥35				
TBIL(μmol/L)	>17.1	1.234(0.861-1.769)	p=0.251		
	≤17.1				
PT(s)	>13.5	0.626(0.346-1.134)	p=0.122	0.652(0.358-1.189)	p=0.163
	<13.5				
AFP (ng/ml)	>400	1.177(0.828-1.673)	p=0.363	1.086(0.758-1.557)	p=0.651
	≤400				
Main tumor size(cm)	≥10	1.015(0.722-1.427)	p=0.933		
	<10				
PVTT	Present	1.201(0.859-1.680)	p=0.285	1.090(0.773-1.535)	p=0.624
	Absent				
Distant metastasis	Present Absent	1.430(1.003-2.038)	p=0.048	1.580(1.099-2.272)	p=0.014

79.3%, p=0.189). Table 5 provides a comprehensive list of the adverse events experienced by the two groups. Hand-foot skin reaction (40.5% vs 1.1%, p< 0.001), Vomiting (64.7% vs 46.7%, p= 0.01), and Rash (43.1% vs 2.2%, p< 0.001) showed slightly higher incidence rates in the combination therapy group compared to the HAIC group, although these differences were not statistically significant. However, the prevalence of Hypoalbuminemia was significantly higher in

Table 5 Adverse Reaction Tables of Patients in Both Groups

	Any grade (cases)			Grade 3–4 (cases)		
Adverse event	**Combination therapy (*n*=116)**	**HAIC (*n*=92)**	***P***	**Combination therapy (*n*=116)**	**HAIC (*n*=92)**	***P***
Leukopenia	14 (12.1%)	9 (0.10%)	0.602	2 (1.7%)	0	–
Thrombocytopenia	18 (15.5%)	13 (14.1%)	0.780	2 (1.7%)	2 (2.2%)	0.815
Hand–foot skin reaction	47 (40.5%)	1 (1.1%)	<0.001	1 (0.8%)	0	—
Increased Creatinine	7(6.0%)	3(3.3%)	0.353	2 (1.7%)	0	—
Vomiting	75(64.7%)	43 (46.7%)	0.01	3 (2.6%)	2 (2.2%)	0.847
Diarrhoea	10 (8.6%)	4 (4.3%)	0.222	1 (0.8%)	0	–
Abdominal pain	71 (61.2%)	45(48.9%)	0.076	3 (4.3%)	2 (2.2%)	0.396
Elevated ALT/AST	100 (86.2%)	73 (79.3%)	0.189	3 (2.6%)	1 (1.1%)	0.434
Hyperbilirubinemia	44(37.9%)	44(47.8%)	0.151	3 (2.6%)	4 (4.3%)	0.484
Hypoalbuminemia	77 (66.4%)	74(80.4%)	0.024	7 (9.5%)	5 (5.4%)	0.277
Rash	50(43.1%)	2(2.2%)	<0.001	2(1.7%)	0	–
Hypertension	89(76.7%)	2(2.2%)	<0.001	3	0	–
Albuminuria	63(54.3)	0	–	17	0	–
Immune-related pneumonia	7(6.0%)	0	-	1	0	-
Immune-related hepatitis	5(4.3%)	0	-	0	0	-
Hypothyroidism	35(30.2%)	0	-	3	0	-

Note: Values are presented as *n* (%). *P* values were calculated using a two-sided χ^2 test.

Table 6 Follow-Up Treatment After Initial Combination Therapy in the Two Treatment Groups

Type	**Combination therapy**	**HAIC**	***p***
Surgical resection	32	5	<0.001
TACE	52	9	<0.001
Iodine 125 seed implantation	3	0	–
SBRT	8	5	0.665
Ablative therapies	13	4	0.073
Cytokine-induced killer cells infusion	2	0	-

Note: Values are presented as *n* (%). *P* values were calculated using a two-sided χ^2 test.

the HAIC group compared to the combination therapy group (61.0% vs 81.7%). Additionally, when considering grade 3–4 adverse events overall, there was a slightly higher occurrence observed in the combination therapy group as opposed to the HAIC group (25.0% vs 17.4%, p = 0.186).

Follow-Up Treatments

The treatment options in both groups are presented in Table 6. There was a significant disparity observed between the two groups regarding surgical resection and TACE, while no notable distinction was found in the remaining treatment modalities. The rate of surgical conversion was considerably higher at 13.4% compared to 3.7%, p< 0.001.

Discussion

In our study, we found that the utilization of HAIC in combination with TKIs and PD-1 inhibitors demonstrates a favorable safety profile and effectively addresses the treatment needs of individuals diagnosed with uHCC. The outcomes of PSM analysis indicate that this combined therapy outperforms the use of HAIC alone in individuals with liver cancer.

In Asian regions, HAIC is widely recognized as a significant treatment method for uHCC patients. Subsequent investigations have aimed to enhance the efficacy of addressing unresectable HCC by incorporating targeted and immune therapies into HAIC.[19–21] Nonetheless, the network meta-analysis report suggests that the advantages in terms of survival

are restricted. HAIC has been acknowledged by the Japanese Society of Hepatology (JSH) as a viable treatment alternative for advanced HCC. According to Zhang et al,[22] the combination of HAIC, camrelizumab, and apatinib demonstrated a significantly higher ORR of 77.1% (95% CI: 59.9%-89.6%) and a disease control rate of 97.1% (95% CI: 85.1%-99.9%) in treating advanced HCC patients. The median progression-free survival was recorded at 10.38 months (95% CI: 7.79–12.45). Luo[23] reported that when HAIC was combined with PD-1 inhibitors and TKIs, it achieved an optimal ORR of 57.2%, along with a DCR of 89.7% based on mRECIST criteria, while maintaining a median overall survival period of approximately 9.7 months. Against this backdrop, Hepatic Arterial Infusion Chemotherapy (HAIC) has become increasingly important in the management of unresectable Hepatocellular Carcinoma (uHCC). Some studies have highlighted HAIC's crucial role in the treatment of patients who develop resistance to TACE or fail first-line systemic therapies, significantly extending the survival of patients with uHCC.[24,25] Compared to the currently recommended refined TACE, HAIC not only improves tumor control rates but is also simpler to administer, facilitating its broader application.

While TACE is commonly recommended as the primary treatment for advanced HCC patients based on guidelines, it can also be utilized as a neoadjuvant therapy prior to liver transplantation. However, repeated embolization may lead to the development of drug resistance due to MAPK activation caused by TP53 mutation and pathways associated with apoptosis. Additionally, studies have revealed that TRT7 hinders the transcriptional activity of P53 through deacetylation, thereby promoting the progression of liver cancer. The expression of TAT7 has been found to exhibit a strong correlation with resistance towards TACE.[26]

In our research, the combination therapy group exhibited superior overall response rates and enhanced overall survival compared to the HAIC group. The improved survival benefits observed in the combination therapy group can be attributed to the ability of FOLFOX-based HAIC treatment to increase levels of chemotherapeutic agents specifically at the tumor site, leading to tumor necrosis. Sequential administration of TACE after HAIC enables precise control over the tumor, aiming for maximum reduction and necrosis. This process releases a significant amount of antigen following tumor necrosis. When combined with PD-1 immune checkpoint inhibitors, this stimulates the immune system for optimal effects. Additionally, TKIs not only inhibit tumor angiogenesis but also reverse vascular endothelial growth factor-mediated impairment of dendritic cell maturation while suppressing activity of macrophages associated with tumors. Consequently, combination therapy extends patient survival and effectively improves prognosis. Previous studies have reported mOS ranging from 18–24 months and mPFS between 6–11 months for triple therapy in primary liver cancer.[27–30] The low incidence of portal vein cancer embolus and distant metastases among the patients in our study may account for this phenomenon.

Research has indicated that the combination therapy of HAIC, lenvatinib, and toripalimab can lead to an elevation in peripheral blood CCL28 levels as well as an increase in the number of CD8+ and CD4+ T cells. Furthermore, this treatment approach has been found to decrease beta-cytokine levels, effectively impeding tumor angiogenesis and progression. Moreover, individuals with high CCL28 expression demonstrated a significant rise in PD-1 and lenvatinib targets. Subgroup analysis revealed that the group with elevated CCL28 levels experienced a notably prolonged mOS.[31] Long et al[32] The study discovered that the combination therapy of TKIs and PD-1 inhibitors, administered through either TACE (TTP) or HAIC (HTP), led to a mPFS of 15 months in the HTP group and 6 months in the TTP group (p=0.028). Moreover, there were intrahepatic relapse rates of 94.1% and 80% (p=0.07), respectively, for these treatment approaches among patients with HCC.

While the combination of TKIs, PD-1 inhibitors, and HAIC has shown promising efficacy in treating patients with uHCC, the occurrence of portal vein tumor thrombosis (PVTT) remains relatively infrequent among individuals undergoing this combined therapeutic approach. This poses a challenge for further treatment in uHCC patients with PVTT. In the group receiving the combination therapy, a small proportion of 8 out of 116 patients (6.9%) subsequently underwent stereotactic body radiation therapy (SBRT) and achieved successful local control. It is worth exploring whether better outcomes can be achieved by combining HAIC/TACE with ablation therapy, SBRT, or iodine-125 particle implantation; however, additional research is required to investigate this possibility.[33–35]

There exist several limitations in this study. Firstly, it is a retrospective analysis and may be influenced by certain biases, which cannot be completely eliminated even with the application of PSM analysis. Secondly, the sample sizes for

each patient group are relatively limited, impeding further investigation. Thirdly, patients included in our study were administered different types of TKIs and anti-PD-1 drugs, potentially resulting in variations in treatment effectiveness. Additionally, discrepancies existed in the follow-up treatments between the two groups, possibly introducing survival bias.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study met the requirements of the declaration of Helsinki and was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. Informed consent for all patients was waived by the committee due to the retrospective nature of this study. All included patients' personal information is strictly confidential.The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

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

This study was supported by the Lanzhou City science and technology development guidance plan(2023-ZD-61).

Disclosure

The authors declare no conflicts of interest in this work.

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