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The safety and efficacy of tyrosine kinase inhibitors and programmed cell death protein-1 inhibitors combined with HAIC/TACE in the treatment of recurrent unresectable hepatocellular carcinoma

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Abstract

Background and aims Hepatocellular carcinoma (HCC) frequently recurs after surgical treatment, necessitating effective postoperative recurrence management for improved long-term patient outcomes. Currently, no standardized treatment approach exists for recurrent unresectable HCC. This study aims to investigate the safety and efficacy of combining tyrosine kinase inhibitors (TKIs) and programmed cell death protein-1 (PD-1) inhibitors with hepatic arterial infusion chemotherapy (HAIC) or transarterial chemoembolization (TACE) in the treatment of recurrent unresectable HCC.

Methods A retrospective analysis was conducted on clinical data from 83 patients diagnosed with unresectable recurrent HCC. Patients were categorized into three groups based on their treatment regimens: HAIC combined with TKIs and PD-1 inhibitors (HTP), TACE combined with TKIs and PD-1 inhibitors (TTP), and TACE alone. Treatment efficacy and safety were compared among these groups, and potential risk factors were identified.

Results The median progression-free survival (PFS) for patients in the HTP group, TTP group, and TACE alone group was found to be 13.7, 9.2, and 2.5 months ($p=0.001$, $p=0.002$). According to the mRECIST criteria, the disease control rates (DCR) in the HTP, TTP and TACE groups was 89.7%, 75.0%, 50.0% ($p=0.002$); objective response rates (ORR) was 44.8%, 35%, 14.7% ($p=0.037$); and complete response (CR) was 17.2%, 0, 0 ($p=0.005$). No serious adverse reactions were observed in the HTP and TTP groups.

Conclusion The HTP and TTP groups were safe and effective compared to TACE alone for the treatment of recurrent unresectable hepatocellular carcinoma, and the HTP group demonstrated a superior CR.

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Keywords Hepatocellular carcinoma, Unresectable recurrence, Hepatic arterial infusion chemotherapy, Transarterial chemoembolization, Tyrosine kinase inhibitors, Programmed cell death protein- 1 inhibitors

Introduction

Liver cancer ranks as the sixth most prevalent cancer and stands as the third leading cause of cancer-related fatalities worldwide [1]. Hepatocellular carcinoma (HCC) constitutes approximately 90% of primary liver cancers. While surgery remains the primary therapeutic approach for HCC patients, the formidable recurrence rate following surgery presents a substantial clinical challenge. Previous investigations have demonstrated a 5-year recurrence rate of approximately 70% for early-stage HCC after surgical resection [2, 3]. The recurrence within 2 years after radical surgery for hepatocellular carcinoma is considered as early recurrence, which usually appears in the vicinity of the resected lesion due to intrahepatic metastasis of the primary tumour [4]. Elevated alpha-fetoprotein (AFP), multiple tumours, tumour size, satellite nodules, and vascular invasion are strongly associated with post-surgical recurrence of hepatocellular carcinoma in patients [5–7]. Due to the complexity of liver cancer recurrence, the choice of recurrence treatment is even more tricky, and safe and effective therapies that can prolong survival and improve life treatment for recurrent patients need to be continuously explored.

Currently, there is no consensus on the optimal treatment regimen for patients confronting unresectable recurrent HCC. An increasing number of scholars are exploring options for recurrence treatment, with liver transplantation, re-hepatic resection, local ablation, hepatic artery chemoembolisation (TACE), and systemic therapies being applied to patients with recurrent hepatocellular carcinoma [8–12]. Liver transplantation for recurrent hepatocellular carcinoma resulted in overall recurrence-free survival rates of 84.8%, 68.2%, and 68.2% at 1, 3, and 5 years postoperatively, respectively, exceeding the UCSF transplantation criteria, tumour diameter ≥ 5 cm, and time to recurrence ≥ 1 year were associated with recurrence after liver transplantation [13]. Roayaie et al. analysed second hepatectomy for recurrent hepatocellular carcinoma and the 5 year overall survival rate after the second resection was 67% but was only used in 15% of patients [14]. Chen et al. showed that radiofrequency ablation had similar 1, 3 and 5 year overall survival rates to repeat hepatic resection in their study of recurrence treatment [15]. Due to the complexity of postoperative recurrence, only a small number of patients have the opportunity to undergo surgery again, and often the recurrence is accompanied by a large number of tumours, multilobar distribution, vascular invasion, extrahepatic metastases, thus seriously affecting the prognosis of patients with recurrent liver cancer. The most commonly used treatment option for recurrent hepatocellular carcinoma is TACE, which can be used for multiple recurrent lesions in the early stage liver that are not amenable to radical surgery or ablative therapy [16, 17]. Patients with recurrence after initial hepatectomy treated with TACE had overall survival rates of 72.9%, 51.8% and 31.8% at 1, 2 and 3 years, with the number of tumours ≥ 2 in the initial hepatectomy, the number of recurrent tumours ≥ 2 and the diameter > 5 cm, and the number of TACEs being the main factors affecting survival rates [18]. With the advent of the era of combination therapies, TACE in combination with systemic therapy has also been applied in patients with unresectable recurrent HCC, and has achieved some efficacy [19–21]. A multicentre retrospective study showed that the progression-free survival (PFS) of TACE combined with lenvatinib and programmed cell death protein- 1 (PD- 1) inhibitors was 24.1 months, 17.3 months, and 13.7 months compared to TACE combined with lenvatinib and TACE alone, and that the triple combination of TACE showed a better objective remission rate and disease control rate [22].

In recent years, hepatic arterial infusion chemotherapy (HAIC) has been widely used in intermediate and advanced hepatocellular carcinoma, and some studies have shown that it is not inferior to TACE in patients with large vessel invasion [23, 24]. Meanwhile, with the research of more targeted and immune drugs for liver cancer, systemic therapy shows an increasingly important role in the treatment of middle and advanced liver cancer. HAIC-based combination of tyrosine kinase inhibitors (TKIS) and PD- 1 inhibitors has achieved better efficacy in advanced unresectable hepatocellular carcinoma, which has received more and more attention from researchers [25–27]. Based on our previous studies of advanced unresectable HCC, HAIC combined with targeted immunotherapy has achieved better clinical outcomes [28]. In a phase II clinical trial, HAIC in combination with lenvatinib and trenbolizumab demonstrated favourable antitumour effects and safety in patients with high risk factors such as vascular invasion or extrahepatic metastases [29]. There is no previous report on the application of HAIC in recurrent hepatocellular carcinoma. we try to apply HAIC combination therapy in recurrent unresectable

hepatocellular carcinoma, hoping to achieve good efficacy therapy, prolonging survival and improving quality of life, and becoming a new treatment option.

Therefore, this study intends to explore the safety and efficacy of HAIC combined with TKIs and PD- 1 inhibitors compared to TACE combined with TKIs and PD- 1 inhibitors and TACE alone in the treatment of patients with recurrent unresectable HCC.

Materials and methods

Patients

This retrospective study enrolled patients diagnosed with HCC who experienced recurrence and had unresectable HCC following radical liver resection at the First Affiliated Hospital of Nanchang University, Nanchang, China, from May 2018 to May 2023. A total of 83 patients who received one of the following treatment regimens were included in the study: HAIC combined with TKIs and PD- 1 inhibitors (HTP), TACE combined with TKIs and PD- 1 inhibitors (TTP) or TACE alone regimen. Inclusion criteria encompassed: (1) Age >18 years; (2) Child–Pugh A or B; (3) Eastern Cooperative Oncology Group Physical Performance Scale (ECOG PS) scores of 0 or 1; (4) Recurrence of hepatocellular carcinoma after radical hepatectomy with pathological confirmation of hepatocellular carcinoma; (5)Not receiving any HCC-related treatment (including but not limited to local therapy, molecular targeted therapy, immune checkpoint inhibitor therapy, etc.); (6) have imaging results to evaluate the tumour. Exclusion criteria consisted of: (1) Presence of other types of tumors; (2) Patients with hepatic encephalopathy or esophageal and gastric varices bleeding; (3) Patients who underwent re-hepatectomy after recurrence; (4) Patients with a history of immunodeficiency disease activity or disease history; (5) Patients lost to follow-up.

Through multidisciplinary team (MDT) discussions, personalized treatment plans were formulated for hepatocellular carcinoma patients. The interventional strategy was selected based on the patient's tumor burden, liver function status, and overall condition, with dynamic adjustment of treatment frequency and regimens.

HAIC procedure

HAIC was administered by femoral artery puncture using the Seldinger technique under local anesthesia. Digital subtraction angiography was performed to delineate the blood supply to the tumor. Subsequently, a 2.7 F microcatheter was positioned for continuous infusion of the chemotherapeutic agent into the tumor-feeding artery. Chemotherapeutic agents included the FOLFOX regimen (HAIC combined with oxaliplatin (OXA), 5-fluorouracil (5-FU), and leucovorin) and the RALOX regimen (HAIC combined with OXA + raltitrexed). The microcatheter was connected externally to an arterial infusion pump, and medication was administered in the ward over a 2-day period. Specific drug dosages were adjusted based on the patient's Child–Pugh classification and tolerance levels.

TACE procedure

Under local anesthesia, the femoral artery was punctured using the Seldinger technique. and a 2.7-F microcatheter was inserted into tumor-feeding artery of the liver by super-selective catheterization. Initially, iodine oil (2–20 mL), epirubicin (20–60 mg), and lopressor (50 mg) were injected into the target vessel under Digital Subtraction Angiography (DSA) fluoroscopic guidance. Subsequently, gelatin sponge particles were introduced into the tumor blood supply artery. Embolization was carried out under DSA fluoroscopic guidance until arterial flow was occluded. Finally, hepatic artery angiography was performed to verify successful embolization.

TKIs and PD- 1 inhibitors

Based on drug availability and the patient's financial circumstances, TKIs such as sorafenib, lenvatinib, and donafenib, and PD- 1 inhibitors like sintilimab, camrelizumab, and tislelizumab were utilized. Drug administration followed established guidelines, with dose adjustments or discontinuations made based on patient baseline conditions, and PD- 1 inhibitor immunotherapy was administered every 3 weeks.

Follow-up, outcome, and safety assessments

Patients were monitored from the initiation of post-relapse treatment until December 2023. Baseline data were collected upon admission and included gender, age, ECOG PS score, presence of hepatitis-B virus infection, cirrhosis status, Child–Pugh classification, AFP levels, tumor size, number of tumors, vascular invasion, extrahepatic metastasis, time of recurrence, and initial surgical clinicopathological information. In the H-T-P group, patients underwent 1–5 consecutive HAIC sessions at 3-week intervals. During each session, blood routine, liver function, AFP, and coagulation function were monitored. Abdominal enhanced computed tomography (CT), magnetic resonance imaging (MRI), and lung CT was performed to assess tumor response. Similarly, patients in the TTP and TACE alone groups received basic condition and tumor assessments after TACE treatment. Subsequent imaging and blood tests were conducted every 4–6 weeks following treatment initiation for all groups until disease progression or death. Treatment efficacy was evaluated using progression-free survival (PFS), disease control rate (DCR), and objective response rate (ORR).

Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and modified RECIST (m-RECIST) based on abdominal CT, MRI, and lung CT. PFS was defined as the duration from the start of treatment after recurrence until tumor progression, death, or last follow-up. DCR represented the percentage of patients achieving complete remission (CR), partial remission (PR), or stable disease (SD). ORR indicated the percentage of patients achieving CR and PR. Safety assessments included the identification of treatment-related adverse events (AEs) based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

Data were analyzed using SPSS 26.0 and R 4.2.1. Categorical variables were presented as n (%), continuous variables that conform to normal distribution are expressed as mean (standard deviation) and continuous variables with skewed distributions are expressed as median (interquartile range). Categorical variables were assessed using the $\chi 2$ test or Fisher's exact test, while continuous variables were evaluated using t-tests and nonparametric tests. Kaplan–Meier analysis and the log-rank test were employed to assess PFS. The Cox proportional hazards model was used for multivariate analysis, and included variables were tested for proportional hazards assumptions. Variables with $p < 0.1$ in univariate analysis were further included in multivariate analysis, with a significance level set at $p < 0.05$ for determining statistically significant differences.

Results

Patient characteristics

Figure 1 illustrates the flow of patients in this study. Initially, 106 patients with recurrent HCC after primary hepatectomy between May 2018 and May 2023 were considered. After initial screening, 19 patients were excluded for various reasons: 2 with other types of tumors, 3 with hepatic encephalopathy or concurrent esophagogastric variceal bleeding, 4 with a history of immunodeficiency disease activity or disease history, and 10 who underwent hepatectomy again after recurrence. During ongoing follow-up, 4 additional patients were lost to follow-up. Ultimately, the study included 83 patients for further analysis, comprising 29 in the HTP group, 20 in the TTP group, and 34 in the TACE alone group.

Table 1 summarizes the baseline data of the patients. Among the included patients, the vast majority were male patients (75/83, 90.36%), with a mean age of 55.70(10.736), and 84.3% had hepatitis B. Notably, there was a significant difference in the number of patients with number of intrahepatic tumours >3, presence of extrahepatic metastases, time to recurrence ≥ 2 years, and pathology with satellite nodules ($p = 0.0071$, $p = 0.0161$, $p = 0.0140$, $p = 0.0398$). the HTP group had more patients with more than 3 tumors, extrahepatic metastases, recurrence time ≥ 2 years and satellite nodules at recurrence

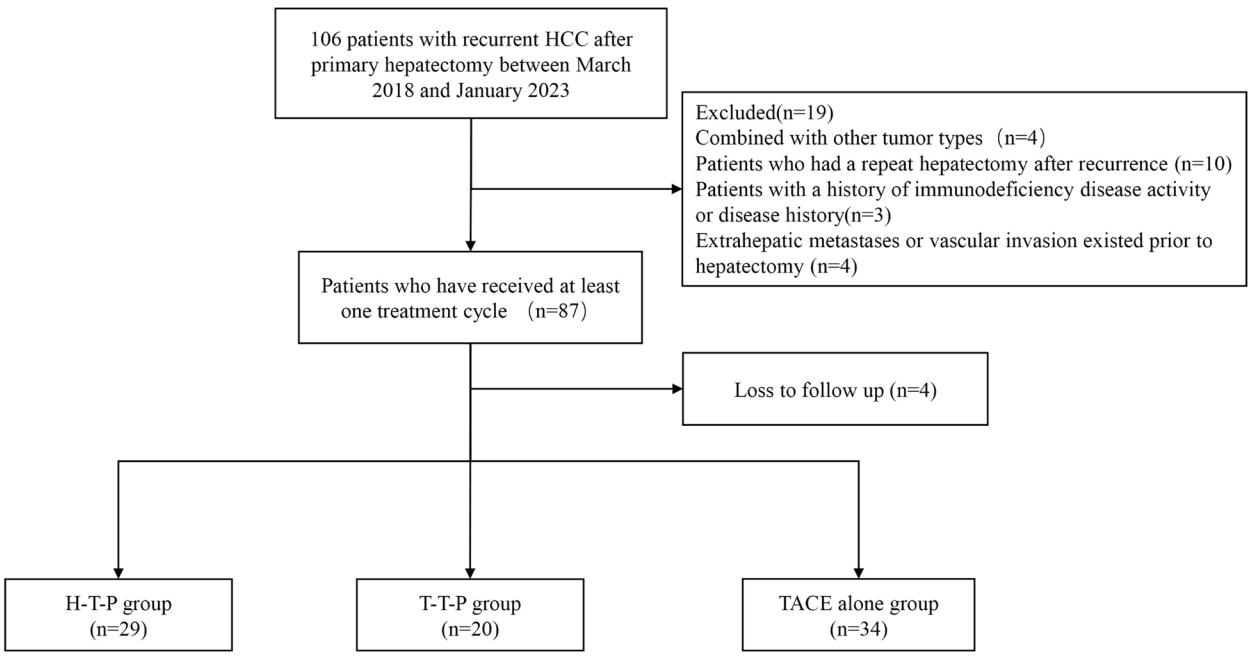

Fig. 1 Flowchart

Table 1 Patient and clinicopathologic characteristics

Characteristic	HTP group ($n = 29$)	TTP group ($n = 20$)	TACE alone group ($n = 34$)	*p*-value
Sex				0.6261
Male	27 (93.10)	17 (85.00)	31 (91.18)	
Female	2 (6.90)	3 (15.00)	3 (8.82)	
Age (years)				0.7676
Mean (SD)	54.48 (10.43)	56.05 (11.68)	56.41 (10.69)	
Hepatitis B surface antigen				0.8248
Positive	25 (86.21)	16 (80.00)	29 (85.29)	
Negative	4 (13.79)	4 (20.00)	5 (14.71)	
Liver cirrhosis				0.5544
Yes	19 (65.52)	10 (50.00)	20 (58.82)	
No	10 (34.48)	10 (50.00)	14 (41.18)	
AFP (ng/mL)				0.9183
< 400	23 (79.31)	15 (75.00)	27 (79.41)	
≥ 400	6 (20.69)	5 (25.00)	7 (20.59)	
ALT (U/L)				0.4888
Median (IQR)	25.60 (33)	28.50 (24)	25.65 (17)	
AST (U/L)				0.3848
Median (IQR)	34.60 (29)	32.60 (19)	27.55(16)	
GGT (U/L)				0.1051
Median (IQR)	112.60 (135.85)	88.74 (89.70)	57.44 (70.00)	
ALP (U/L)				0.3106
Mean (SD)	122.93(98.55)	101.36 (48.62)	95.81 (53.83)	
PT (s)				0.0488
Mean (SD)	11.92 (0.92)	12.01 (1.13)	12.55 (1.17)	
Number of intrahepatic lesions (n)				0.0071
≤ 3	5 (17.24)	8 (40.00)	19 (55.88)	
> 3	24 (82.76)	12 (60.00)	15 (44.12)	
Maximum diameter of intrahepatic tumor (cm)				0.4604
≤ 5	24 (82.76)	16 (80.00)	31 (91.18)	
> 5	5 (17.24)	4 (20.00)	3 (8.82)	
Vascular invasion				0.4294
Yes	2 (6.90)	0 (0.00)	1 (2.94)	
No	27 (93.10)	20 (100.00)	33 (97.06)	
Extrahepatic metastases				0.0161
Yes	7 (24.14)	6 (30.00)	1 (2.94)	
No	22 (75.86)	14 (70.00)	33 (97.06)	
Time to recurrence after surgery				0.0140
< 2	20 (68.97)	13 (65.00)	32 (94.12)	
≥ 2	9 (31.03)	7 (35.00)	2 (5.88)	
ALBI grade				0.7215
1	12 (41.38)	11 (55.00)	19 (55.88)	
2	16 (55.17)	9 (45.00)	14 (41.18)	
3	1 (3.45)	0 (0.00)	1 (2.94)	
ECGO PS				NA
0	29 (100.00)	20 (100.00)	34 (100.00)	
Child–Pugh				0.5352
A	27 (93.10)	20 (100.00)	32 (97.06)	
B	2 (6.90)	0 (0.00)	1 (2.94)	
Pre-operative AFP (ng/mL)				0.7429

Table 1 (continued)

Characteristic	HTP group (*n* = 29)	TTP group (*n* = 20)	TACE alone group (*n* = 34)	*p*-value
< 400	18 (62.07)	14 (70.00)	24 (70.59)	
≥ 400	11 (37.93)	6 (30.00)	10 (29.41)	
Microvascular invasion				0.9676
M0	15 (51.72)	9 (45.00)	16 (47.06)	
M1	9 (31.03)	7 (35.00)	10 (29.41)	
M2	5 (17.24)	4 (20.00)	8 (23.53)	
Tumor differentiation				0.6757
Low	6 (20.69)	3 (15.00)	9 (26.47)	
Middle	22 (75.86)	15 (75.00)	24 (70.59)	
High	1 (3.45)	2 (10.00)	1 (2.94)	
Satellite nodule				0.0398
Yes	8 (27.59)	0 (0.00)	6 (17.65)	
No	21 (72.41)	20 (100.00)	28 (82.35)	

ECOG PS Eastern Cooperative Oncology Group performance status, *AFP* alpha-fetoprotein, *ALBI* albumin-bilirubin; Calculated using the following equation: linear predictor = (log10 bilirubin mmol/L × 0.66) + (albumin g/L × − 0.085). The continuous linear predictor was further categorized into three different grades for prognostic stratification purposes: grade 1 (less than − 2.60), grade 2 (between − 2.60 and − 1.39) and grade 3 (above − 1.39), *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* γ-glutamyl transpeptidase, *ALP* Alkaline phosphatase, *PT* prothrombin time, *TACE* transarterial chemoembolization, *HTP* hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TTP* transarterial chemoembolization combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors

compared to the TACE alone group. The rest had no statistically significant difference at baseline. As shown in Table 2, HAIC treatment regimens included FOLFOX and RALOX, while TKIs consisted of lenvatinib, donafenib, and sorafenib. PD- 1 inhibitors administered were camrelizumab, sintilimab, and tislelizumab. In the HTP group, the treatment regimens involving TKIs and PD- 1 inhibitors included the following combinations: Lenvatinib + camrelizumab ($n = 13$), lenvatinib + stintilimab ($n = 5$), lenvatinib + tislelizumab ($n = 3$), sorafenib + camrelizumab ($n = 5$), donafenib + camrelizumab ($n = 3$). In the TTP group, the treatment regimens involving TKIs and PD- 1 inhibitors included the following combinations: Lenvatinib + camrelizumab ($n = 13$), Lenvatinib + stintilimab ($n = 1$), Lenvatinib + tislelizumab ($n = 1$), sorafenib + camrelizumab ($n = 2$), donafenib + camrelizumab ($n = 3$). The median cycles treatment of HAIC and TACE were 2 and1.

Table 2 Regimens of therapy

	Treatment	No. (%)
HAIC regimen		
	FOLFOX	20 (69)
	RALOX	9 (31)
HTP group		
	Lenvatinib + Camrelizumab	13(44.8)
	Lenvatinib + stintilimab	5(17.2)
	Lenvatinib + tislelizumab	3(10.3)
	sorafenib + camrelizumab	5(17.2)
	donafenib + camrelizumab	3(10.3)
TTP group		
	Lenvatinib + Camrelizumab	13(65.0)
	Lenvatinib + stintilimab	1(5.0)
	Lenvatinib + tislelizumab	1(5.0)
	sorafenib + camrelizumab	2(10.0)
	donafenib + camrelizumab	3(15.0)
HAIC treatment cycle		
	Median (range)	2(1–6)
TACE treatment cycle		
	Median (range)	1(1–3)

HAIC hepatic arterial infusion chemotherapy, *FOLFOX* HAIC with oxaliplatin, 5-fluorouracil, and leucovorin, *RALOX* HAIC with raltitrexed plus oxaliplatin, *HTP* hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TTP* transarterial chemoembolization combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TACE* transarterial chemoembolization

Outcomes

The median follow-up times in the HTP, TTP, and TACE alone groups were 19.0, 24.1, and 21.7 months, respectively. Median PFS was significantly longer in the HTP group (13.7 months) and the TTP group (9.2 months) compared to the TACE alone group (2.5 months) ($p = 0.001$, $p = 0.002$; Fig. 2). The HTP and TTP groups significantly prolonged PFS compared with the TACE group alone, and there was no significant difference in progression-free survival between the HTP and TTP groups($p = 0.96$). The median OS was 15.5

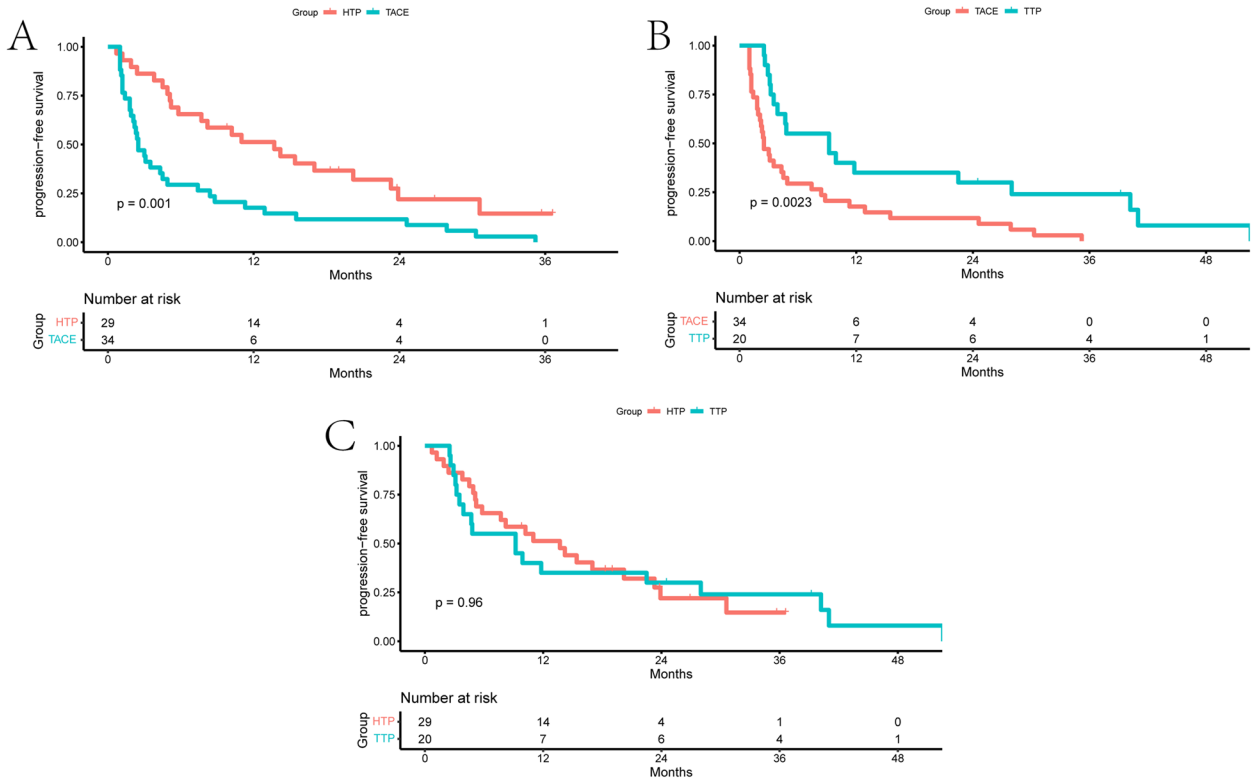

Fig. 2 Kaplan–Meier curves of cumulative PFS in recurrent HCC patients; **A**, HAIC combined with TKIs and PD- 1 inhibitors versus TACE alone; **B**, TACE combined with TKIs and PD- 1 inhibitors versus TACE alone; **C**, HAIC combined with TKIs and PD- 1 inhibitors versus TACE combined with TKIs and PD- 1 inhibitors

months in the TACE group, and the median OS was achieved in both the HTP and TTP groups, which due to the relatively short follow-up duration (Fig S1).

The best response outcomes were evaluated according to RECIST1.1 and m-RECIST criteria (Table S1). According to m-RECIST, in the HTP, TTP, and TACE alone groups, the DCR was 89.7%, 75.0%, and 50.0% ($p=$ 0.002), the ORR was 44.8%, 35%, and 14.7% ($p=$ 0.037), and the CR was 17.2%, 0, and 0 ($p=$ 0.005). Both the HTP and TTP groups showed significantly better DCR and ORR compared to the TACE alone group. Furthermore, the CR rate in the HTP group was superior to that in the TTP group and the TACE alone group.

Remarkably, five patients in the HTP group achieved CR, including one patient with multiple intrahepatic lesions, abdominal metastases, and lung metastases. Nine months after hepatectomy, this patient experienced recurrence and subsequently received HAIC in combination with sorafenib and camrelizumab. Remarkably, during the treatment course, all intrahepatic and abdominal metastases completely disappeared, and lung lesions exhibited complete necrosis. During the subsequent follow-up, no progression of intrahepatic and metastatic lesions was observed, resulting in a PFS of 35.7 months (Fig. 3).

Analysis of factors affecting PFS

We conducted an analysis to identify potential factors that could impact the PFS of patients with unresectable recurrent HCC. Initially, we performed univariate analysis using the clinicopathological data of the patients (Table 3). Subsequently, variables with p-values less than 0.1 in the univariate analysis were included in the multivariate analysis. The results showed that in HTP vs TACE, AFP ≥400 ng/ml [hazard ratio (HR) 2.55, 95% confidence interval (CI) 1.19–5.47, $p=$ 0.016], PT (HR 1.33, 95% CI 1.02–1.75, $p=$ 0.036), microvascular invasion (HR 1.60, 95% CI 1.05–2.43, $p=$ 0.027), HTP regimen (HR 0.29, 95% CI 0.15–0.55, $p<$ 0.001). In TTP vs TACE, AFP ≥400 ng/ml (HR 4.18, 95% CI 1.71–10.18, $p=$ 0.002), PT (HR 1.30, 95% CI 1.03–1.65, $p=$ 0.029), microvascular invasion (HR 1.56, 95% CI 1.06–2.28, $p=$ 0.024), and TTP regimen (HR of 0.27, 95% CI 0.13–0.56, $p<$ 0.001). Thus, this suggests that AFP ≥400 ng/ml, PT and microvascular invasion are independent risk factors for PFS and HTP with TTP regimen is an independent protective factor for PFS (Table 4).

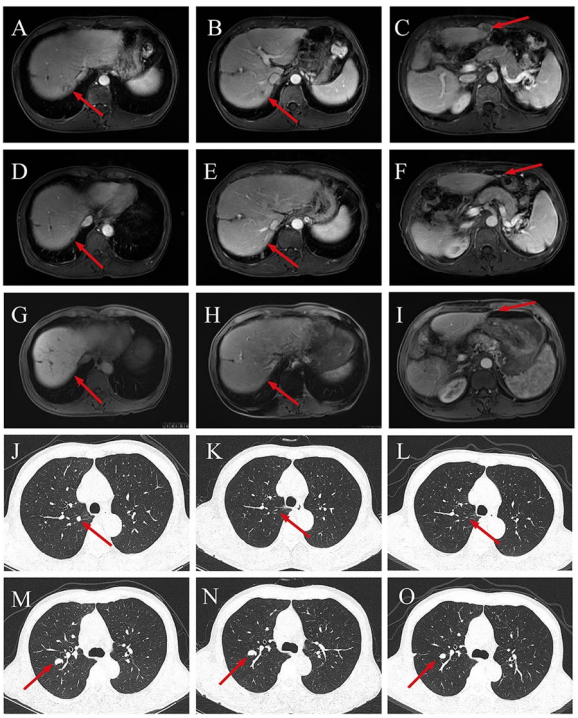

Fig. 3 MRI and CT of the abdomen of the patient. **A**–**C**, J, M, before receiving HAIC triple treatment. **D**–**F**, K, N, after receiving HAIC triple therapy. **G**–**I**, L, O, Latest review results. The arrow points to the change in recurrent lesions

Treatment-related AEs

Table S2 summarizes the most common treatment-related adverse reactions observed in each treatment group. In the HTP group, the most prevalent adverse reactions included abdominal pain, elevated AST and ALT levels, and leukopenia. The TTP group exhibited increased AST and ALT levels, abdominal pain, and decreased platelet counts as the most common adverse reactions. In the TACE alone group, the primary adverse reactions were abdominal pain, vomiting, and elevated AST and ALT levels. Notably, the HTP group had a higher proportion of patients experiencing leukopenia. Grade 3/4 adverse reactions were observed in only a small subset of patients in all three groups, and there were no statistically significant differences among them. Importantly, no deaths related to adverse reactions occurred in any of the three treatment groups.

Discussion

The recurrence of HCC following surgery poses a significant challenge to long-term patient survival. While some HCC patients with intrahepatic recurrence may undergo radical surgery, thereby extending their survival, those with recurrent HCC involving multiple intrahepatic lesions, vascular invasion, or extrahepatic metastases lose the opportunity for surgery and face a poorer prognosis [14, 30, 31]. Many studies have shown that the risk factors for early recurrence after radical resection of HCC are microvascular invasion, narrow margins (< 1.0 cm), multiple tumors, satellite nodules, tumor diameter >5 cm, and poorly differentiated tumor [32, 33]. In a study by Xu et al. comparing the efficacy of different adjuvant treatment regimens in patients at high risk of recurrence after radical resection of hepatocellular carcinoma,

Table 3 Univariate Analysis Associated with Progression-free Survival

Variables	Univariate Analysis	
	HR (95% CI)	*p*-value
Male	1.32(0.53–3.28)	0.556
Age	0.99(0.97–1.01)	0.328
Hepatitis B surface antigen Positive	0.88(0.44–1.78)	0.724
Liver cirrhosis	0.94(0.58–1.52)	0.803
AFP ≥ 400 ng/mL	2.60(1.47–4.61)	0.001
ALT	0.92(0.53–1.59)	0.754
AST	0.94(0.55–1.60)	0.818
GGT	0.75(0.47–1.20)	0.230
ALP	1.07(0.59–1.97)	0.817
PT	1.25(1.02–1.54)	0.036
Number of intrahepatic lesions > 3	1.03(0.63–1.67)	0.911
Maximum diameter of intrahepatic tumor > 5 cm	1.03(0.52–2.03)	0.928
Vascular invasion	1.97(0.47–8.15)	0.352
Extrahepatic metastases	0.56(0.28–1.14)	0.110
Time to recurrence after surgery ≥ 2	0.48(0.25–0.89)	0.021
ALBI grade (1/2/3)	1.20(0.78–1.84)	0.411
ECGO PS (0)	-	-
Child–Pugh (A/B)	1.21(0.38–3.86)	0.748
Pre-operative AFP ≥ 400 ng/mL	0.77(0.46–1.29)	0.321
Microvascular invasion(M0/M1/M2)	1.29(0.97–1.72)	0.080
Tumor differentiation (L/M/H)	0.65(0.39–1.11)	0.113
Satellite nodule	2.00(1.07–3.73)	0.029
HTP vs TTP	0.79(0.40–1.58)	0.510
HTP vs TACE	0.34(0.19–0.60)	0.001
TTP vs TACE	0.40(0.21–0.73)	0.003

AFP alpha-fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* γ-glutamyl transpeptidase, *ALP* Alkaline phosphatase, *PT* prothrombin time, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ALBI* albumin-bilirubin, Calculated using the following equation: linear predictor = (log10 bilirubin mmol/L × 0.66) + (albumin g/L × − 0.085). The continuous linear predictor was further categorized into three different grades for prognostic stratification purposes: grade 1 (less than − 2.60), grade 2 (between − 2.60 and − 1.39), and grade 3 (above − 1.39), *HTP* hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TTP* transarterial chemoembolization combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TACE* transarterial chemoembolization, *HR* hazard ratio, *CI* indicates confidence interval

Table 4 Multivariate Analysis Associated with Progression-free Survival

Variables	Multivariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
AFP ≥ 400 ng/mL	2.55(1.19–5.47)	0.016	4.18(1.71–10.18)	0.002
PT	1.33(1.02–1.75)	0.036	1.30(1.03–1.65)	0.029
Time to recurrence after surgery ≥ 2	0.81(0.33–2.00)	0.644	0.99(0.43–2.27)	0.984
Tumor differentiation (L/M/H)	1.60(1.05–2.43)	0.027	1.56(1.06–2.28)	0.024
Satellite nodule	1.09(0.52–2.32)	0.813	0.47(0.16–1.37)	0.166
HTP vs TACE	0.29(0.15–0.55)	< 0.001	-	-
TTP vs TACE	-	-	0.27(0.13–0.56)	< 0.001

AFP alpha-fetoprotein, *PT* prothrombin time, *HTP* hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TTP* transarterial chemoembolization combined with tyrosine kinase inhibitors and programmed cell death protein- 1 inhibitors, *TACE* transarterial chemoembolization, *HR* hazard ratio, *CI* indicates confidence interval

postoperative adjuvant transhepatic arterial chemoembolisation, postoperative adjuvant hepatic arterial infusion of chemotherapy, postoperative adjuvant radiotherapy, and postoperative adjuvant molecularly-targeted therapies were all effective in reducing the rate of postoperative recurrence and significantly improving survival and disease free survival [34]. Atezolizumab in combination with bevacizumab improves recurrence-free survival in patients with high-risk recurrent HCC in the IMbrave050 study [35].

The treatment of recurrent HCC is also in the exploratory stage. A propensity-matched study indicated that 5-year OS was 41.6% and 30.2% ($p = 0.028$), and 5-year PFS was 21.3% and 15.8%, respectively, for recurrent intermediate-stage hepatocellular carcinoma treated with TACE alone or combined with ablation ($p = 0.024$) [36]. Another study of sorafenib alone versus a combination of TACE and radiofrequency ablation for advanced recurrent hepatocellular carcinoma showed a median OS of 14 months vs 9 months and a median progression-free time of 7.0 months vs 4.0 months after both treatments [37]. Meanwhile, a study of TACE in combination with lenvatinib and PD- 1 inhibitor for the treatment of recurrent unresectable HCC demonstrated superior efficacy of TACE in combination with systemic therapy compared with TACE alone [22]. Therefore, the combination of local and systemic therapy has shown promising results in the treatment of recurrent HCC. HAIC, as an emerging technology, has significant efficacy in advanced hepatocellular carcinoma, and whether it can further improve the prognosis of patients with recurrent HCC is not yet reported in the literature [38–40]. In this study, HAIC combined with TKIs and PD- 1 inhibitors was applied to treat patients with recurrent unresectable HCC. The HAIC triplet regimen in this study demonstrated similar efficacy to the TACE triplet regimen, and significantly improved PFS, DCR, and ORR compared with TACE treatment alone. During our follow-up, only the HTP group had five CR patients, and there were no CR patients in both the TTP and TACE-only groups, reflecting the good tumor control effect of the HTP regimen. We observed that a higher proportion of patients in both the HTP and TTP groups exhibited high-risk factors, including number of intrahepatic tumors > 3, extrahepatic metastases, time to recurrence ≥ 2 years, and satellite nodules. Notably, these patients underwent triple therapy, which significantly prolonged the time to recurrence or progression and improved long-term survival. These results further underscore the advantages of the triple therapy regimen in patients with recurrent unresectable HCC.

HAIC is a method of continuous perfusion of chemotherapeutic drugs into the tumor blood supply arteries for anti-tumor effects, circumventing the first-pass effect of the liver, enhancing local drug concentration and reducing the systemic toxicity of chemotherapeutic drugs [41]. First, cytotoxic chemotherapeutic agents can have an anti-tumor effect by inducing apoptosis, which enhances the sensitivity of cytotoxic T cells [42, 43]. Decreasing immunosuppression in the tumor microenvironment (TME) through a process known as immunogenic cell death (ICD) of tumor cells [44, 45]. Second, the anti-angiogenic effects of vascular endothelial growth factor (VEGF) can synergize with the anti-tumor effects of immune checkpoint inhibitors such as PD- 1 by modulating immune suppression and regulating the TME [46, 47].

In our study, AFP ≥ 400 ng/ml at relapse, PT and microvascular invasion were independent risk factors affecting PFS.AFP and microvascular invasion have been suggested to be strongly associated with survival in relapsed patients in many studies, which is consistent with the results of the present study [22, 48, 49]. The results suggest that we should take into account the

patient's AFP level as well as PT in the course of relapse treatment, and also note the presence of microvascular invasion, which may have an impact on the patient's outcome.

The safety and toxicity of the treatment is a key issue that should not be ignored in either the triplet therapy group or the TACE alone group. Hepatic impairment, abdominal pain, and vomiting were the more common adverse effects in all three groups, and leukopenia alone occurred in a greater proportion of patients in the HTP group than in the other two groups, but did not cause more grade 3/4 adverse effects. There were no deaths due to side effects in any of the three groups. This suggests that the triplet therapy group has controllable toxicities compared with the TACE group alone, but the use of TKI drugs as well as PD- 1 inhibitors may lead to a certain degree of bone marrow suppression as well as a certain burden on liver function. Changes in blood routine and liver function should be closely monitored during treatment, and drug dosage should be dynamically adjusted.

This retrospective, single-center study has several limitations: (1) The HTP and TTP regimens did not exhibit a significant difference in median PFS, possibly due to the relatively small number of cases and a shorter follow-up period. Further research with extended follow-up and a larger sample size is warranted. (2) The study included patients from a single center, potentially introducing confounding biases. (3) The follow-up period was relatively short, and a comparison of differences in overall survival (OS) could not be made. Therefore, future studies should aim to expand the sample size and conduct multicenter randomized controlled trials to validate the efficacy of the treatment approach presented in this study.

Conclusion

In conclusion, both the HTP and TTP regimens demonstrated superior DCR, ORR, and longer PFS compared to TACE alone in the treatment of recurrent unresectable HCC. Notably, the HTP regimen achieved a higher CR rate compared to the TTP regimen, and there was no observed increase in severe toxicities with the triple regimen compared to TACE alone. Additionally, an AFP $\geq$400 ng/ml at recurrence, PT and microvascular invasion at recurrence was identified as an independent risk factor for reduced PFS. This study introduces new treatment options for recurrent unresectable HCC.

Abbreviations

TKIs	Tyrosine kinase inhibitors
PD- 1	Programmed cell death protein 1
TACE	Transarterial chemoembolization
HAIC	Hepatic arterial infusion chemotherapy
DCR	Disease control rates
ORR	Objective response rates
CR	Complete response
PFS	Progression-free survival
HCC	Hepatocellular carcinoma
HTP	HAIC combined with TKIs and PD-1 inhibitors
TTP	TACE combined with TKIs and PD-1 inhibitors
ECOG PS	Eastern Cooperative Oncology Group performance status
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	γ-Gamma-glutamyl transferase
ALP	Alkaline Phosphatase
PT	Prothrombin time
ALBI	Albumin-bilirubin
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
M-RECIST	Modified response Evaluation Criteria in Solid Tumors
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1. Table S1. Tumor best response outcomes

Supplementary Material 2. Table S2. Treatment-related adverse events (TRAEs)

Supplementary Material 3. Fig S1. Kaplan–Meier curves of cumulative OS in recurrent HCC patients

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Authors' contributions

Study concept and design: Wei Deng, Jin Xie, Tao Wang, Zhigao Hu and Renfeng Shan. Acquisition and analysis or interpretation of data: Wei Deng, Jin Xie, Tao Wang, Zhigao Hu and Renfeng Shan. Drafting of the manuscript: Wei Deng, Guoqing Zhu, Yongqiang Xiao, Jiahao Tao, Liucong Lin and Yu Liu. Critical revision of the manuscript: Tao Wang, Renhua Wan, Zhigao Hu, and Renfeng Shan. Statistical analysis: Wei Deng, Jin Xie, Laihui Luo, Wu Wen, Bin Yu, Minglong Wang, Tao Wang and Xian Ge. Administrative and technical support: Rongguang Luo, Renhua Wan, Zhigao Hu, and Renfeng Shan. All authors contributed to the article and approved the submitted version.

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Data availability

The data that support the results of this study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the first affiliated hospital of Nanchang University, Nanchang, China. No. (2022) CDYFYYLK (06–009). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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