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ARTICLE

Hepatic arterial infusion chemotherapy combined with lenvatinib and PD-1 inhibitor for treating unresectable hepatocellular carcinoma

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Abstract

Aims/Background The combination of lenvatinib and programmed cell death protein 1 (PD-1) inhibitor has demonstrated significant efficacy in treating unresectable hepatocellular carcinoma. Our study aimed to evaluate the safety and efficacy of triple therapy that includes hepatic arterial infusion chemotherapy, lenvatinib and PD-1 inhibitor for treating unresectable hepatocellular carcinoma.

Methods Patients with a primary diagnosis of advanced hepatocellular carcinoma between June 2020 and August 2023 were included in this study. Initially, 53 patients with hepatocellular carcinoma were enrolled. Then, 13 patients were excluded based on the inclusion criteria, resulting in 40 patients included for analysis. Among them, 31 patients received triple therapy, including 16 Barcelona Clinic Liver Cancer C stage, 12 Barcelona Clinic Liver Cancer-B, and 3 Barcelona Clinic Liver Cancer-A hepatocellular carcinoma patients. The primary endpoint was the objective response rate, while the secondary endpoints included the conversion resection rate, pathological complete response rate, pathological partial response rate, and treatment-related adverse events.

Results The objective response rate was 80.65% at a median follow-up of 24.5 months (range: 12.6–55.8 months). Of the 14 patients (45.2%) who underwent conversion therapy and were eligible for surgery, 7 patients underwent liver resection and the remaining 7 patients underwent liver transplantation. The median interval between the start of triple therapy and surgery was 117 days, ranging from 25 to 215 days. The pathological complete response was observed in six patients (19.4%) and the pathological partial response rate in eight patients (25.8%). All adverse events occurred in 77.4% of the patients.

Conclusion In patients with unresectable hepatocellular carcinoma, the combination of hepatic arterial infusion chemotherapy, lenvatinib, and PD-1 inhibitor exhibits favourable efficacy and well tolerability, achieving a desirable pathological complete response rate while maintaining manageable drug toxicity.

Key words: Hepatic arterial infusion chemotherapy; Lenvatinib; PD-1 inhibitor; Unresectable hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) stands as the predominant form of primary liver cancer in China contributing to approximately half of the global incidence of new HCC cases (Yang et al, 2019; Chidambaranathan-Reghupaty et al, 2021). Less than 10% of patients with advanced HCC survive more than 5 years (Feng et al, 2024). Surgery is the first-line treatment for HCC and often remains the only approach to improve the prognosis of patients. However, a significant number of primary diagnosed HCC patients are at the middle and late stages (Ganesan and Kulik, 2023). 80% of patients with HCC at primary diagnosis have unresectable tumour size (Wu et al, 2023b). Consequently, strategies to downstage unresectable hepatocellular carcinoma (uHCC) to achieve a resectable tumour size have become a focal point of research (Liu et al, 2021).

In recent years, systemic chemotherapy has introduced new treatment possibilities for patients with uHCC, leading to notable improvements in patient outcomes (Luo et al, 2021). In terms of effectiveness and survival rates, studies have demonstrated that

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combination therapy outperforms monotherapy (Liu et al, 2019; Donne and Lujambio, 2023; Yang et al, 2023a). Various combination treatment options have shown promise in improving patients' outcomes and have the potential to transform uHCC into a resectable one. Current management of uHCC includes transarterial chemoembolization (TACE), transarterial radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), targeted therapy, immunotherapy or their combinations. The combination of lenvatinib (LEN) and immune checkpoint inhibitors (ICIs) has exhibited a promising anti-tumour efficacy in patients with uHCC. A real-world study of levatinib in combination with programmed cell death protein 1(PD-1) inhibitor therapy demonstrated long-term survival and considerable Objective response rate (ORR) and Disease control rate (DCR) in Chinese uHCC patients (Yang et al, 2023b). A study showed TACE combined with levatinib offers optimal treatment for uHCC (Zhang et al, 2022). Moreover, the addition of HAIC to this combination (ICIs+LEN+HAIC) provides superior survival benefits in patients with PD-L1 positive uHCC (Pan et al, 2021). Our study aimed to evaluate the efficacy and safety of triple therapy (HAIC+LEN+PD-1) based on real-world data.

Methods

Patient enrolment

A total of 53 uHCC patients were retrospectively enrolled with a primary diagnosis of advanced HCC at Sun Yat-sen Memorial Hospital, Sun Yat-sen University between June 2020 and August 2023. Due to various reasons, 13 patients were excluded. Of the remaining 40 patients, the final study analysis included 31 who underwent triple therapy (Figure 1). 40 patients with uHCC received conversion therapy. 31 patients received triple therapy (HAIC+LEN+PD-1), with 10 patients receiving pembrolizumab 200 mg (Batch no. SJ20180019, MSD Ireland, Kenilworth, NJ, USA), 4 patients receiving tislelizumab 200 mg (Batch no. S20190045, Baiji Shenzhou Biopharmaceutical Co., Guangzhou, Guangdong, China), and 17 patients receiving sintilizumab 200 mg (Batch no. S20180016, Cinda Biopharmaceutical Co., Suzhou, Jiangsu, China). Of the 31 patients, the median age was 55.26 ± 9.52 years old, and 3 were classified as BCLC stage A, 12 as stage B, and 16 as stage C HCC. This study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University. The ethics number is SYSKY-2023-1116-01. Patients provided written informed consent and agreed to the inclusion of all relevant data in the study.

The radiological criteria of the Chinese HCC staging guidelines and the histological features of the tumour serve as the basis for HCC diagnosis (Sidali et al, 2022). The diagnostic criteria are as follows: (a) two imaging examinations indicating typical HCC features, (b) one imaging examination indicating typical HCC features along with an alpha-fetoprotein > 400 ng/mL. According to the Liver Cancer Study Group of Japan, uHCC is characterised by single or multiple large tumours invading more than one lobule or major arteries (Kudo et al, 2024). The definition of conversion to resectable HCC is as follows: (a) adequate liver volume after R0 resection, and (b) resection with favourable biological and oncological features (Arita et al, 2022).

The analysis included patients who met the following criteria: (a) patients with uHCC receiving triple therapy (HAIC+LEN+PD-1); (b) aged between 18 and 75 years; (c) tolerable to treatment; (d) had a target lesion that exhibited changes according to the modified response evaluation criteria in solid tumours (mRECIST) (Llovet and Lencioni, 2020); (e) Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0–1; The exclusion criteria are following: (a) patients received any treatment related to HCC before enrolment; (b) the absence of previous treatment and follow-up data; (c) patients unable to tolerate the triple therapy.

Procedures of conversion therapy

LEN (Batch no. HJ20200044, Eisai Co., Ltd, Tokyo, Japan) was administered orally once per day, with a dosage of 8 or 12 mg (< 60 kg, 8 mg/day; ≥ 60 kg, 12 mg/day) depending on the patient's body weight. PD-1 was intravenously injected every 3 weeks. The specific

dosages for each of the three PD-1s were as follows: sintilizumab 200 mg, pembrolizumab 200 mg, or tislelizumab 200mg. MFOLFOX6 therapy was administered as follows: hepatic arterial administration delivered oxaliplatin (Batch no. H20010615, Yakou Pharmaceutical Co., Chongqing, China) at a dosage of 110 mg/m^2; accompanied by intra-arterial infusion of 5-FU (Batch no. H20051626, Zhuo Tai Pharmaceutical Co., Haikou, Hainan, China) at a dosage of 2.4g/m^2 for 46 h. An enhanced abdominal computed tomography (CT, ME2403141CT) or Magnetic Resonance Imaging (MRI, NA240124NMR) was performed every 3–5 weeks and HAIC was conducted if the hepatic artery had an obvious blood supply. Treatment was discontinued if patients had disease progression, treatment-related toxicity, death, or withdrawal.

Response and assessments

Based on Response Evaluation Criteria in Solid Tumours (RECIST 1.1) (Wahl et al, 2009) and mRECIST, investigators employed contrast-enhanced CT or MRI scans every 3– 5 weeks to classify the tumour response into four categories: complete response (CR), partial response (PR), stable disease (SD) and progressing disease (PD). The overall response rate was determined by adding the CR and PR rates. The DCR was determined by adding the CR, PR, and SD rates. The response period was measured from the start of triple treatment until they met PR or CR criteria. Pathological complete response (pCR) and pathological partial response (pPR) were defined as the complete absence of tumour cells and 10%– 50% of surviving tumour cells, respectively (Klassen-Fischer and Neafie,

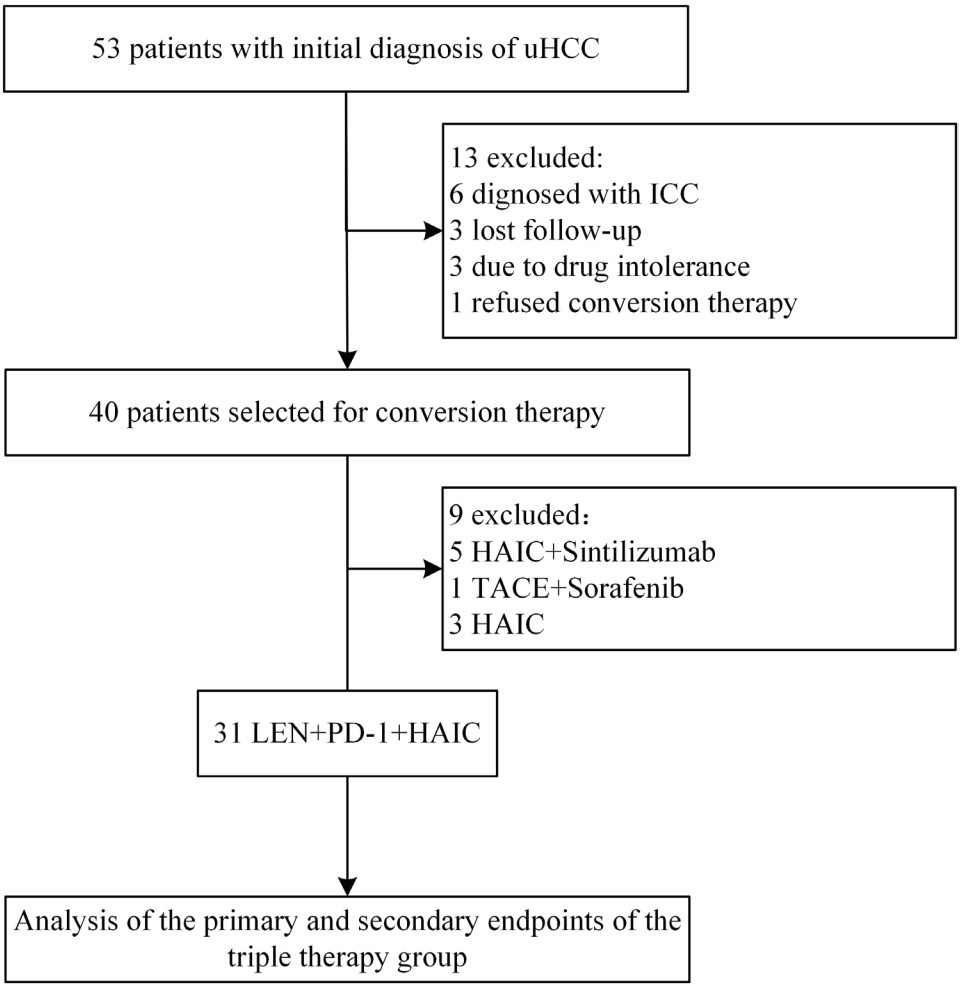

Figure 1. Flow chart of inclusion, exclusion and grouping criteria for this study. uHCC, unresectable hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinama; HAIC, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; LEN, lenvatinib; PD-1, programmed cell death protein 1.

2016). According to the Common Terminology Criteria for Adverse Events version 5.0, adverse events (AEs) were extracted from patients' inpatient medical records for analysis (Freites-Martinez et al, 2021).

Follow-up

The follow-up duration ranged from 2 to 4 months, during which clinical trial-related data were recorded. Strict adherence to medication regimens was ensured. Liver resection or liver transplantation was performed by the same surgical team once the tumour conversed to a resectable one. Patients were excluded when they developed progressing disease, progressive symptoms, and intolerable toxicity. All treatment decisions for each patient were made after the multidisciplinary consultation.

Statistical analyses

SPSS (version 26, Chicago, IL, USA) was used for statistical analyses. Categorical data were presented as N (%). Continuous variables that did not follow a normal distribution were expressed as medians (ranges). The Kaplan-Meier method was used to estimate survival probability, and comparisons between groups were made using the Log-rank test. The p-value < 0.05 represented a significant difference.

Results

Characteristics of the patients

This study enrolled 53 patients with unresectable liver cancer between June 2020 and August 2023. Portal vein invasion was observed in 15 patients (48.39%), while 7 patients (22.58%) had hepatic vein tumour thrombus. The median tumour size at the baseline was 7.90 cm (range: 1.80–19.40 cm). Furthermore, 4 patients (12.90%) had extrahepatic metastases. Table 1 shows the patient demographics and baseline characteristics.

Tumour response and conversion after triple therapy

The median follow-up time was 24.5 (12.6–55.8) months. Based on the two evaluation criteria, the primary endpoints of ORR were 26 (83.87%) and 25 (80.65%), respectively (Table 2). There were 0 CR, 26 PR (83.8%), 1 SD (3.2%), and 4 PD (12.9%) according to RECIST criteria, and 10 CR (32.3%), 15 PR (48.4%), 4 SD (12.9%), and 2 PD (6.5%) according to mRECIST criteria. The DCR was 87.09% (27/31) and 93.55% (29/31) according to RECIST and mRECIST criteria, respectively. The median time between triple therapy initiation and surgery was 117 (25–215) days. Of the two evaluation criteria, the secondary endpoint of the study demonstrated that 14 patients (45.16%) successfully converted to surgical treatment, including 7 patients (22.58%) receiving liver resection and 7 patients (22.58%) receiving liver transplantation. The waterfall plot demonstrated the analysis of tumour reduction in 27 patients (87.09%) and 29 patients (93.55%) after receiving triple therapy (HAIC+LEN+PD-1) (Figure 2). Patients in the surgical group after triple therapy (HAIC+LEN+PD-1) had better prognosis than those in the non-surgical group in Figure 3 (p=0.0457). A typical case after triple therapy is shown in Figure 4. A 56-year-old male patient initially diagnosed with giant hepatocellular carcinoma experienced a significant reduction in tumour size after four cycles of HAIC+LEN and PD-1 therapy. The efficacy of this method in reducing the extent of the tumour is evident.

Pathological response after triple therapy (HAIC+LEN+PD-1)

In the 31 patients, 6 (19.4%) and 8 (25.8%) patients achieved pCR and pPR after surgery, respectively. The overall pathological response rate was 45.2% (14/31). Based on the tumour regression grade criteria (TRG, Mandard) (Hirohata et al, 2021), TRG can be categorised into 5 grades after surgery: grade 1 refers to complete regression (no fibrosis of tumour cells detected); grade 2 means to fibrosis with scattered tumour cells; grade 3 refers to more tumour cells with predominantly fibrosis; grade 4 suggests more tumour cells than fibrosis; grade 5 indicates tumour tissue with no regressive changes. There were

Table 1. Baseline characteristics of patients

Variables	Number (n=31)
Age, years	
≤ 65	26(83.87%)
> 65	5(16.13%)
Gender	
Male	31 (100%)
Female	0
BMI (kg/m²)	
Normal	22(70.97%)
Abnormal	9(29.03%)
ECOG PS	
0	28(90.32%)
1	3(9.68%)
HBV	
Positive	27(87.10%)
Negative	4(12.90%)
HBV-DNA (IU/mL)	
≤ 500	10(32.26%)
> 500	21(67.74%)
Pre-treatment AFP (ng/mL)	
≤ 400	17(54.84%)
> 400	14(45.16%)
Child-Pugh grades, n (%)	
A	23(74.19%)
B	8(25.81%)
Tumour number, n (%)	
Solitary	14(45.16%)
Multiple	17(54.84%)
Median tumour size (cm)	7.90 (4.10, 11.80)
Tumour size, cm, n (%)	
≤ 10	19(61.29%)
> 10	12(38.71%)
Tumour location, n (%)	
Unilobar	22(70.97%)
Bilobar	6(19.35%)
Central	3(9.68%)
Portal vein invasion, n (%)	
Yes	15(48.39%)

Table 1. Baseline characteristics of patients (Continued)	
Variables	**Number (n=31)**
No	16(51.61%)
Hepatic vein tumour thrombus, n (%)	
Yes	7(22.58%)
No	24(77.42%)
Extrahepatic metastasis, n (%)	
Yes	4(12.90%)
No	27(87.10%)
BCLC staging, n (%)	
A	3(9.68%)
B	12(38.71%)
C	16(51.61%)
Pathological response	
pCR	6 (19.4%)
pPR	8 (25.8%)
TRG (grades)	
1	7 (22.6%)
2	4 (12.9%)
3	3 (9.7%)
4	0
5	0

BMI, Body Mass Index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HBV, Hepatitis B virus; AFP, α-fetoprotein; ALT, alanine transaminase; BCLC, Barcelona Clinic Liver Cancer; pCR, pathological complete response; pPR, pathological partial response; TRG, tumour regression grade.

Table 2. Assessment of tumour responses based on RECIST1.1 and mRECIST		
	RECIST1.1	**mRECIST**
Variables	All patients	All patients
DCR	27 (87.09%)	29 (93.55%)
ORR	26 (83.87%)	25 (80.65%)
CRR	7 (22.58%)	7 (22.58%)
CTR	7 (22.58%)	7 (22.58%)

DCR, Disease control rate; ORR, Objective response rate; CRR, conversion resection rate; CTR, conversion transplantation rate; mRECIST, modified response evaluation criteria in solid tumours.

7 (22.6%), 4 (12.9%), 3 (9.7%), 0 (0.0%), and 0 (0.0%) patients who reached grades 1, 2, 3, 4, and 5 respectively (Table 1).

Safety analysis

As shown in Table 3, treatment-related AEs occurred in 24 patients (77.4%) during the follow-up after triple therapy (HAIC+LEN+PD-1). No treatment-related deaths occurred. Elevated aspartate aminotransferase (AST) (90.3%), abdominal pain (64.5%), elevated blood

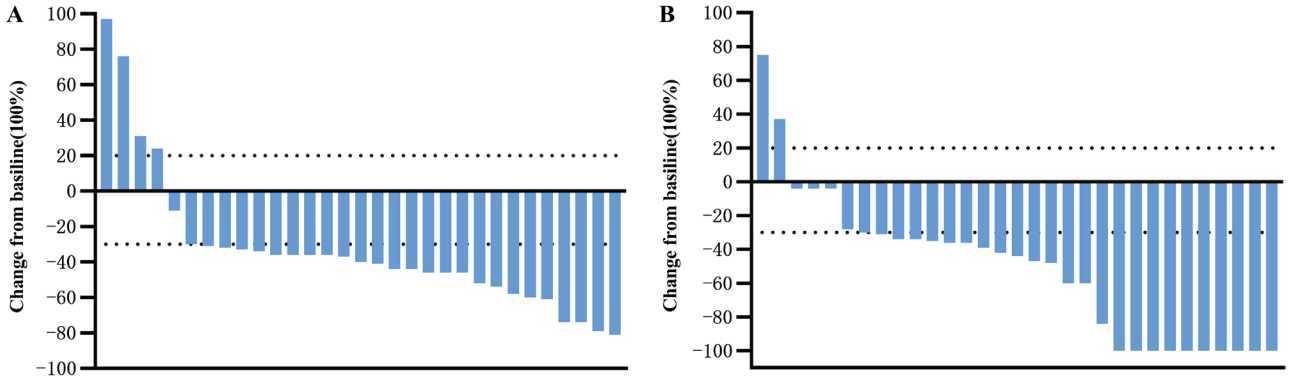

Figure 2. Waterfall plot. The best percentage changes from baseline in the size of the intrahepatic target lesions of patients receiving HAIC+LEN+PD-1. (A) Assessed with RECIST1.1 in patients with image measurements before and after treatment. (B) Assessed with mRECIST in patients with image measurements before and after treatment.

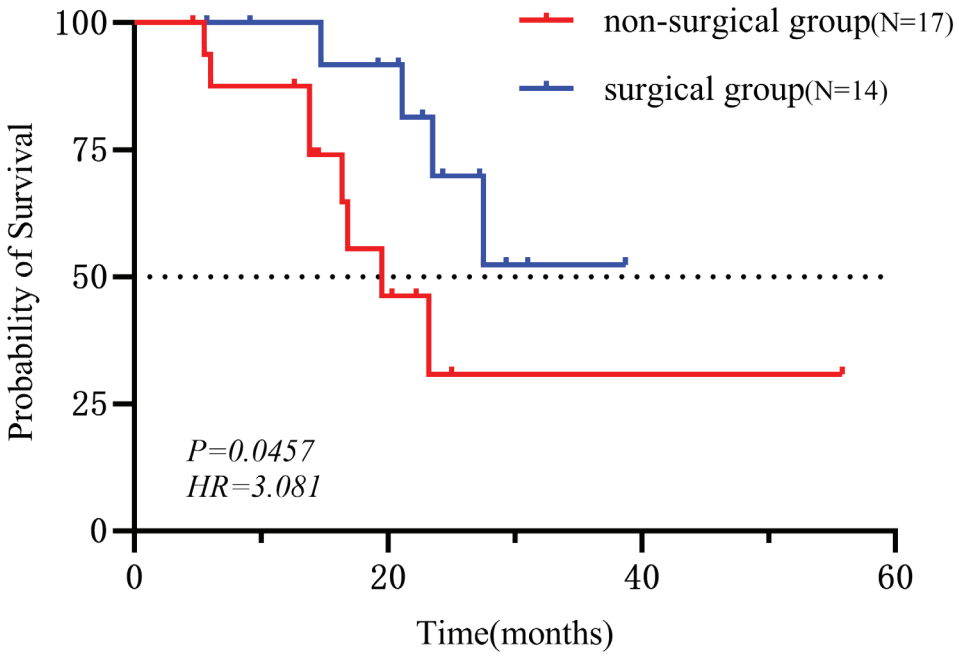

Figure 3. Kaplan-Meier curves for survival probability after stratification by the absence or presence of surgery (LEN+PD-1+HAIC).

bilirubin (61.3%), and alanine aminotransferase (ALT) (61.3%) were the most common AEs. Abdominal pain (64.5%), thrombocytopenia (54.8%), and vomiting (41.9%) were the most common grade 1 to 2 AEs. Most of the liver abnormalities associated with triple therapy (HAIC+LEN+PD-1) were returned to normal after maintenance therapy, such as ALT, AST, and hyperbilirubinemia. Patients with grade 3 AEs recovered with conservative treatment. All AEs were manageable during follow-up.

Discussion

CR, PR, SD, PD, DCR, ORR, conversion resection rate (CRR), and conversion transplantation rate (CTR) were employed to monitor the tumour response rate. The pCR, mPR, pPR, and nPR were used to evaluate the pathological response. The relationship between the amount of residual tumour cells and tissue fibrosis was described using TRG. The clinical safety of drug therapy was assessed by AEs. The ORR, conversion success rate (CRR+CTR), and pathological response rates of the 31 patients included in the triple

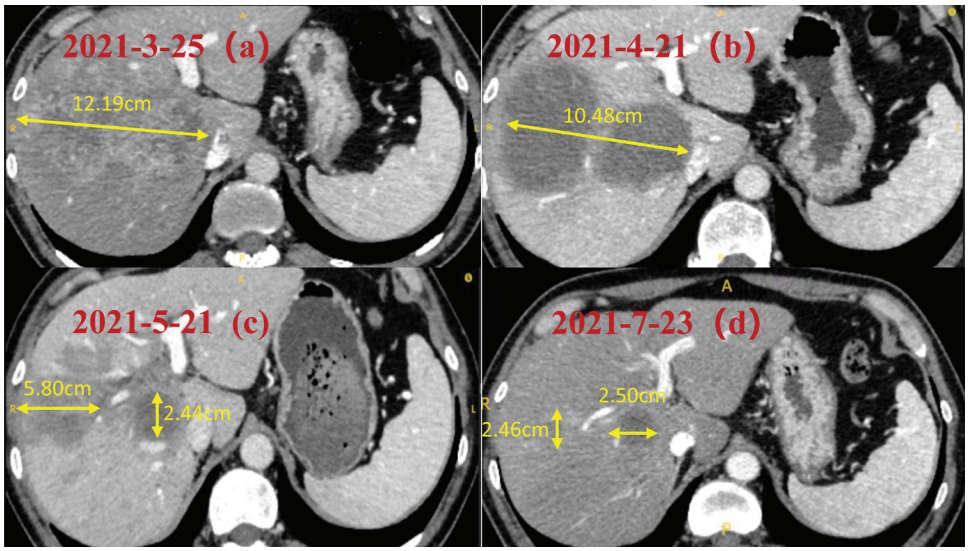

Figure 4. A male, 56 years old, was diagnosed with giant mass hepatocellular carcinoma. Treatment was HAIC+pembrolizumab+Lenvatinib. (a) CT images before triple therapy; (b–d) CT signs after one, two, and four cycles of treatment, respectively. CT, computed tomography.

Table 3. Treatment-related adverse events

Adverse event	Number	Any grade	Grade 1–2	Grade 3
ALT increased	19 (61.29%)	7 (22.58%)	3 (9.68%)	4 (12.90%)
AST increased	28 (90.32%)	15 (48.39%)	6 (19.35%)	9 (29.03%)
Neutropenia	3 (9.68%)	3 (9.68%)	3 (9.68%)	0
Fever	13 (41.94%)	13 (41.94%)	13 (41.94%)	0
Decreased appetite	11 (35.48%)	11 (35.48%)	11 (35.48%)	0
White blood cell count decreased	4 (12.90%)	4 (12.90%)	4 (12.90%)	0
Thrombocytopenia	18 (58.07%)	18 (58.07%)	17 (54.84%)	1 (3.23%)
Weight loss	5 (16.13%)	5 (16.13%)	5 (16.13%)	0
Increased blood bilirubin	19 (61.29%)	10 (32.26%)	10 (32.26%)	0
Fatigue	12 (38.71%)	12 (38.71%)	12 (38.71%)	0
Vomiting	13 (41.94%)	13 (41.94%)	13 (41.94%)	0
Hypertension	7 (22.58%)	7 (22.58%)	7 (22.58%)	0
Hypotension	3 (9.68%)	3 (9.68%)	3 (9.68%)	0
Abdominal pain	20 (64.52%)	20 (64.52%)	20 (64.52%)	0
Diarrhea	4 (12.90%)	4 (12.90%)	4 (12.90%)	0
Proteinuria	1 (3.23%)	1 (3.23%)	1 (3.23%)	0
Hand-foot skin reaction	6 (19.35%)	(19.35%)	6 (19.35%)	0

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase.

therapy (HAIC+LEN+PD-1) were 80.6% (25/31), 45.2% (14/31), and 45.2% (14/31), respectively. The treatment-related AEs were controllable. The waterfall plot indicated that 29 (93.5%) of the patients had a reduction in tumour size. Our study findings indicated

that the combination of HAIC, LEN, and PD-1 was both tolerable and efficacious for uHCC patients.

HAIC can be administered locally through the hepatic artery, resulting in higher concentrations of the drug in the liver and lower concentrations in other organs. HAIC has been extensively adopted in various countries such as Japan and Korea as a treatment option for advanced HCC. Patients with uHCC often have poor prognoses. Zheng et al (2021) first demonstrated the significant superiority of triple therapy over double therapy for treating uHCC. Consistent with their finding, our results indicated that the addition of a HAIC-based triple therapy regimen resulted in a higher ORR (80.6%). Thus, combination therapy based on HAIC is urgently needed.

Recently, HAIC-based combination treatment has attracted interest due to its improvement of patient prognosis and tumour response rates. Hamaoka et al (2017) conducted a study demonstrating that outcomes achieved with HAIC-based therapy were comparable in effectiveness to those achieved with TACE-based therapy. He et al (2019) presented at ESMO Asia that HAIC+TKIs+ICIs exhibited an ORR of 67.6% for advanced HCC, offering a new alternative for HAIC-based conversion therapy. Currently, studies have reported varying results of HAIC-based conversion therapy (CR of 0–48%, ORR of 40%–96%, and DCR of 77.6%– 100%) (Mei et al, 2021; An et al, 2023; Wei et al, 2023), whereas our results were consistent with previous findings. A phase II trial investigating a combination of systemic therapy (LEN and toripalimab) and topical therapy (HAIC) demonstrated a progression-free survival rate of 80.6% at six months. They proposed that triple therapy should be the primary treatment for individuals with advanced uHCC, as it exhibited controllable toxicity and potent anti-tumour activity (Sacchi De Camargo Correia et al, 2024). These results are consistent with those of a retrospective study comparing the anti-tumour activity of HAIC+LEN+PD-1 to LEN+PD-1 in patients with advanced HCC (Mei et al, 2021), indicating that triple therapy exhibited significantly superior antitumor effects.

This study, consistent with the data from multiple studies (Hack et al, 2020; Wu et al, 2023a), demonstrated a high conversion success rate, as evidenced by surgery successfully conducted in all 14 (14/31) converted patients. After surgery, six patients (6/31) achieved pCR. After a successful patient conversion resection, research has demonstrated that the length of tumour-free survival is correlated with the degree of pathological remission, indicating that patients in pathological remission have a better prognosis (Wang et al, 2022). During triple therapy (HAIC+LEN+PD-1), AEs cannot be avoided. In this study, the most concentrated AEs that occurred were elevated AST (90.3%), abdominal pain (64.5%), elevated blood bilirubin (61.3%), and elevated ALT (61.3%). However, despite the increased number of grade 3 AEs, they were all controlled after conservative treatment. Emphasis should be given to preventive strategies for patients experiencing adverse reactions (Marta et al, 2021). For instance, a retrospective study discovered that hand-foot skin reaction and hypertension could serve as markers to predict improved prognosis in LEN-treated HCC patients (Shimose et al, 2020).

Currently, it is acknowledged that combination therapy yields a higher conversion rate than single therapy, and a combination of local and systemic treatments yields higher effectiveness than local or targeted combination immunotherapy (Yang et al, 2023a; Ikuta et al, 2018). HAIC-based combination therapy has demonstrated remarkable anti-tumour effects and improved survival benefits. Based on current research findings, the possible mechanisms of the triple therapy synergistic anti-tumour are as follows: (a) HAIC induces antigenicity of tumour cells through high-concentration chemotherapy drugs, thereby adapting tumour immune microenvironment and promoting the efficacy of systemic therapy; (b) chemotherapeutic drugs may increase antigen presentation and improve T cell-mediated acquired immunity; (c) combining PD-1 inhibitor and anti-vascular endothelial growth factor may facilitate vascular normalisation and disrupt the hypoxic microenvironment of tumours (Voron et al, 2015); (d) TKIs and ICIs can prevent tumour angiogenesis and recurrence.

This study has several limitations. First, due to the small sample size and limited supporting data, this study was conducted retrospectively. Second, in this study, there was no control group to compare the effectiveness and safety of HAIC+LEN+PD-1 with other methods. Third, three anti-PD-1 drugs were used in this study, which might affect the robustness of the results. Our study proposed that close multidisciplinary collaboration

was crucial for tailoring treatments based on individual patients' demands. Furthermore, there should be greater emphasis on patient selection, protocol formulation, efficacy assessment, timing of transformation, and prompt management of AEs. Future research should focus on larger multicenter, prospective, randomised controlled trials to investigate more rational treatments.

Conclusion

In this real-world study, the HAIC+LEN+PD-1 triple therapy is both tolerable and efficacious in treating uHCC patients. This triple therapy exhibits higher tumour response rates, translational resection rates, and pathological remission rates in patients with uHCC under conditions of controlled AEs. Therefore, HAIC+LEN+PD-1 is a promising treatment option for uHCC patients.

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Availability of data and materials

All the data are presented in this paper, and further inquiries can be directed to the respective authors.

Author contributions

The authors' contributions to this study are listed below: (I) Conception and design: CL, XDS. (II) Administrative support: XDS. (III) Provision of study materials or patients: ZHB, XHY, QBT. (IV) Collection and assembly of data: ZHB, XDS. (V) Data analysis and interpretation: ZHB, XDS, RZ, QBT, XHY. (VI) Manuscript writing: All authors. (VII) Revising the manuscript: BZH, SXD. All authors contributed to the article and approved the submitted version. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University. The ethics number is SYSKY-2023-1116-01. Patients provided written informed consent and agreed to the inclusion of all relevant data in the study. This study was conducted in accordance with the Declaration of Helsinki.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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