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ORIGINAL RESEARCH

Safety and Efficacy of TACE-HAIC Combined with Lenvatinib and PD-1 Inhibitors in Large Intermediate-Stage Hepatocellular Carcinoma: A Multi-Center Retrospective Study

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Purpose: This study was designed to compare the safety and efficacy of transarterial chemoembolization (TACE) plus hepatic arterial infusion chemotherapy (HAIC) or TACE combined with lenvatinib (LEN) and PD-1 inhibitors (PD-1i) in large intermediate-stage hepatocellular carcinoma (iHCC).

Methods: This multi-center retrospective study was conducted at four tertiary medical centers. From January 01, 2021, to June 30, 2024, 221 patients with large iHCC undergoing TACE-HAIC-LEN-PD-1i (THLP group, n=103) or TACE-LEN-PD-1i (TLP group, n=118) were enrolled. Local tumor responses, survival, and treatment-related adverse events (TRAEs) were analyzed between the THLP and TLP groups.

Results: Baseline characteristics were well-balanced between the two groups ($P>0.05$). Objective response rate (70.8% vs. 44.9%, $P<0.001$) and disease control rate (91.2% vs. 78.8%, $P=0.011$) in the THLP group were significantly superior over those in the TLP group. Compared to the TLP group, the THLP group achieved significantly better median progression-free survival (11.0 vs. 8.0 months, $P<0.001$) and median overall survival (29.9 vs. 20.3 months, $P<0.001$). The incidence of conversion to resection was obviously higher in the THLP group than that in the TLP group (20.4% vs.9.3%, $P=0.020$). The frequency of any grade or grade 3–4 TRAEs was comparable between the two groups, associating with no statistical differences ($P>0.05$). No grade 5 TRAEs and treatment-related mortality were observed.

Conclusion: TACE-HAIC-LEN-PD-1i was safe and well-tolerated, and achieved better efficacy than TACE-LEN-PD-1i in patients with large iHCC. Further randomized controlled trials are required to validate the benefits of TACE-HAIC-LEN-PD-1i.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine kinase inhibitor, immune checkpoint inhibitor

Introduction

Hepatocellular carcinoma (HCC) is a predominant global public health concern, ranking as the fifth most commonly carcinoma and the second leading cause of cancer-related mortality worldwide.[1] HCC accounts for 75–85% of primary liver cancer cases, with an escalating incidence annually.[1] Surgical resection stands out as the primary therapeutic approach for

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HCC, offering the most promising potential for a definitive cure.[2–4] In clinical practice, approximately 20% to 30% of HCC patients are deemed suitable candidates for curative resection, with a corresponding overall survival (OS) rate of around 18% at five years.[2–4] Intermediate-stage HCC (iHCC) encompasses a notably diverse patient cohort characterized by varying tumor attributes, hepatic function, and performance status. Presently, transarterial chemoembolization (TACE) remains the established standard of care for iHCC according to multiple clinical directives.[2–4] Nonetheless, TACE achieves a mere 10% to 20% complete tumor response rate, owing to the heterogeneous nature of tumors, intricate anatomical considerations, and technical complexities.[2–4]

Novel therapeutic approaches are under investigation to improve outcomes for iHCC. Molecular targeted therapy (MTT) and immunotherapy have emerged as pivotal systemic treatments for HCC.[5–7] The concurrent use of TACE, MTT, and immune checkpoint inhibitor (ICI) is increasingly prevalent for high tumor burden iHCC cases.[7,8] The EMERALD-1 trial demonstrated enhanced progression-free survival (PFS) in unresectable iHCC with combining TACE, durvalumab, and bevacizumab compared to TACE alone.[9] Similarly, the LEAP-012 study revealed superior PFS in non-curable iHCC cases with TACE, lenvatinib (LEN), and pembrolizumab compared to TACE monotherapy.[10] Additionally, recent retrospective research by Moriyama et al indicated improved prognosis in iHCC with atezolizumab plus bevacizumab-TACE sequential therapy versus atezolizumab-bevacizumab monotherapy.[11]

Hepatic arterial infusion chemotherapy (HAIC) has been confirmed as a prominent therapeutic modality for patients with advanced HCC.[12–14] In contrast to systemic chemotherapy, HAIC offers inherent advantages such as targeted delivery of chemotherapeutic agents directly into the hepatic artery, leading to elevated concentrations within the tumor microenvironment. This approach facilitates prolonged interaction between the chemotherapeutic agents and tumor cells while minimizing systemic drug toxicity and preserving normal liver tissue integrity.[12–14] Randomized controlled trials (RCTs) have assessed the feasibility of oxaliplatin, fluorouracil, and leucovorin (FOLFOX)-based HAIC, demonstrating notable survival advantages in the management of advanced HCC, particularly in individuals with extensive tumors and portal vein tumor thrombus (PVTT).[12,13] However, limited research has investigated the safety and efficacy of HAIC for iHCC, and the potential effectiveness of action of HAIC remains incompletely elucidated.

LEN, a molecular targeted drug, has demonstrated reliable efficacy in normalizing tumor vasculature and achieving a higher tumor response rate compared to sorafenib.[15] On the other hand, programmed death 1 inhibitors (PD-1i) are widely recognized as a common immunotherapy for HCC.[16] However, the safety and efficacy of TACE combined with HAIC, LEN, and PD-1i (TACE-HAIC-LEN-PD-1i) in treating large iHCC remain unexplored. To address this gap, we postulated that the combination of HAIC could enhance the efficacy of TACE plus LEN and PD-1i (TACE-LEN-PD-1i). Consequently, we developed this multicenter retrospective study to compare TACE-HAIC-LEN-PD-1i with TACE-LEN-PD-1i for large iHCC. Our study aims to propose a promising combined therapeutic approach for large iHCC.

Methods and Materials

Study Design and Patients

This retrospective study complied with the ethical standards of the Declaration of Helsinki and obtained ethical approval from Sun Yat-sen Memorial Hospital of Sun Yat-sen University (Approval No. SYSKY-2025-723-01). Furthermore, this study was officially registered on ClinicalTrials.gov. Written informed consent was achieved from each participant before any treatment in this study. HCC was diagnosed by the standards of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Between January 01, 2021, and June 30, 2024, 221 patients with large iHCC who underwent TACE-HAIC-LEN-PD-1i or TACE-LEN-PD-1i were enrolled at four tertiary medical centers. The follow-up termination took place on March 31, 2025.

For study participants, the inclusion criteria were (a) age of 18 to 75 years; (b) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (c) Barcelona Clinic Liver Cancer (BCLC) stage B HCC; (d) a maximum tumor diameter of larger than 5 cm; (e) unresectable HCC confirmed by an experienced multidisciplinary team; (f) hepatic function of Child-Pugh class A or B; and (g) availability of medical data for the assessment in this study. Meanwhile, the following exclusion criteria were considered: (a) experiencing other malignancies; (b) any other anti-tumor therapy prior to the study treatment; (c) allergy to the study drugs; (d) existence of autoimmune diseases; (e) any grade of digestive

hemorrhage; (f) uncontrolled comorbidities; and (g) inadequate renal function, bone marrow function, or coagulation function. Patients' flowchart has been demonstrated as Figure 1.

Treatment Protocol

All TACE and HAIC procedures were conducted based on the international or Chinese guidelines and/or consensus.[2,17] In order to avoid serious chemotherapeutic-related adverse events and heterogeneity between conventional TACE (c-TACE) and drug-eluting bead TACE (DEB-TACE), patients who underwent c-TACE were enrolled for assessment. TACE procedures were performed by using digital subtraction angiography (DSA). Routinely, after the indication of hepatic artery angiography, a mixture of epirubicin (30–50 mg) and Lipiodol (10–25 mL) (Lipiodol Ultra-Fluide, Guerbet) was administered into tumor-feeding arteries via 2.6F/2.7F microcatheter (RAPIDTHRU, Hengrui Medical; Progreat, Terumo), followed by the embolization of blank microspheres (150–350 or 350–560 μm) (Hengrui Medical, China). The dosage regimen of chemotherapeutic, Lipiodol, or microspheres was determined depending on patients' body weight and tumor characteristics. The embolization endpoint was defined as feeding vessels exhibiting complete stasis and/or tumor stains disappearing, which was achieved within 2 to 3 cycles of TACE. In the THLP group, HAIC was conducted after TACE treatment. Briefly, after the injection of the Lipiodol mixture and microspheres, a microcatheter was placed in the main tumor-feeding artery. Then, the chemotherapy strategy of oxaliplatin, fluorouracil, and leucovorin (oxaliplatin, 85 mg/m^2, 2 h; leucovorin, 400 mg/m^2, 2 h; flurouracil, 400 mg/m^2 bolus; and 2400 mg/m^2, 46 h) was infused. Even if TACE treatment was discontinued, HAIC was conducted once per 3-week period, and up to eight cycles. For each HAIC treatment, femoral artery puncture and catheterization were performed, and the catheter was removed after the infusion of chemotherapeutics.

All enrolled patients were treated with a LEN regimen of 8 mg (patient weight no more than 60 kg) or 12 mg (patient weight more than 60 kg) daily, initiated within 3 to 5 days following TACE-HAIC or TACE procedure. Following, a PD-

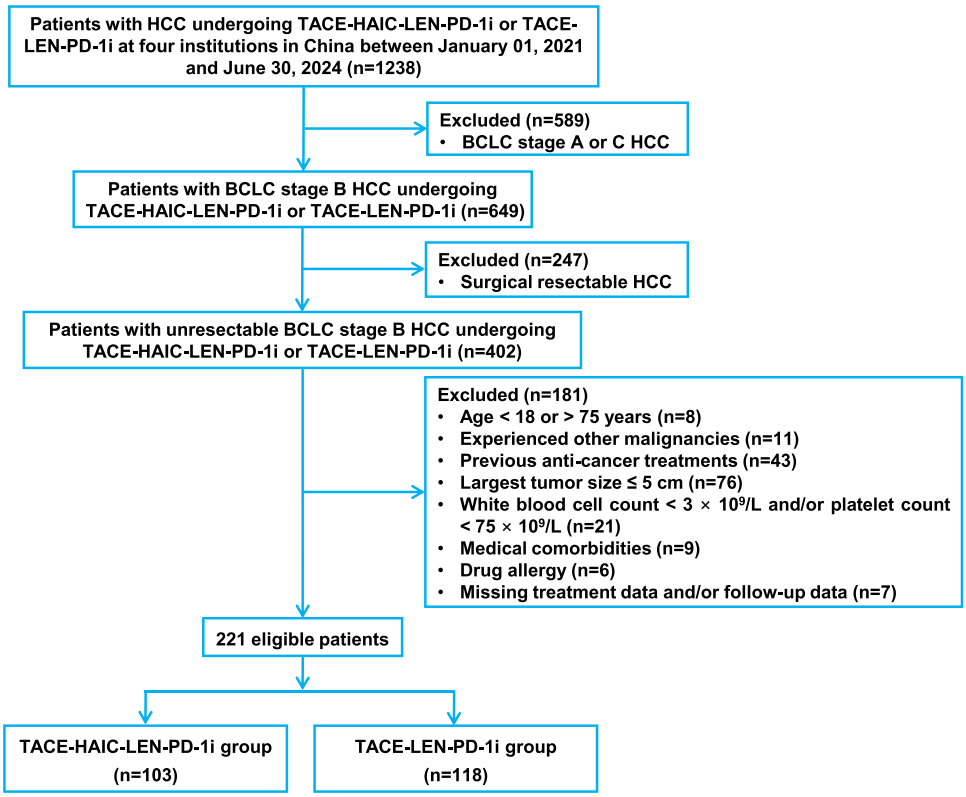

Figure 1 Flowchart of the patients.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, PD-1 inhibitor; BCLC, Barcelona Clinic Liver Cancer.

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1i (including a 200 mg dosage of pembrolizumab, camrelizumab, sintilimab, or tislelizumab; or a 240 mg dosage of toripalimab) was given once per 3-week period. All PD-1i used in this study were selected based on the recommendations by international or Chinese guidelines.[18,19] Systemic treatments were adjusted or halted in cases of intolerable adverse events, or a change of treatment regimen for unmanageable progressive disease (PD).

If sufficient tumor responses were confirmed after the study treatment, conversion resection would be suggested as a curative treatment. When study treatments were concluded, TACE was repeated "on demand" until TACE resistance occurred. In addition, the "second-line" therapies were considered, including local therapies (eg. ablation therapies, ^{125}I seed implantation, or radiotherapy), and systemic therapies (eg. systemic chemotherapy, other MTTs or ICIs).

Efficacy and Safety Evaluation

OS was designed as the primary endpoint, which was calculated from the initial of the study treatments to the last follow-up or death. PFS was considered the secondary endpoint, measuring from the first treatment cycle to the first tumor progression, patient death, or last follow-up. Tumor responses were evaluated by the modified response evaluation criteria in solid tumors (mRECIST). Objective response (OR) contains complete response (CR) and partial response (PR), where disease control (DC) contains CR, PR, and stable disease (SD). Treatment-related adverse events (TRAEs) were assessed by the common terminology criteria for adverse events (CTCAE) version 5.0.

Follow-up

After the study treatments, all patients experienced follow-up every 4 weeks. Imaging examinations (CT and/or MRI) were performed every 4 to 6 weeks following the initial cycle of study treatments to assess tumor status. Laboratory tests, such as liver function and tumor markers, were evaluated concurrently. Tumor responses were analyzed by a multidisciplinary team of radiologists and oncologists with over 10 years of experience in interventional radiology and oncology. After the study treatments, if residual or progressive tumors were observed, options included repeated TACE, a change in MTT or PD-1i, or other alternative treatments such as ablation therapy, ^{125}I seed implantation, radiotherapy, or systemic chemotherapy were considered.

Statistical Analysis

SAS software (version 9.4; SAS Institute) and GraphPad Prism (version 9.5; GraphPad, Inc.) were employed to analyze data and create figures. Mean ± standard deviation (SD) or median [95% confidence interval (CI)] was used to describe continuous data. Categorical data was displayed by frequency. Mann–Whitney *U*-test was utilized to compare continuous variables. Either Pearson's $\chi 2$ test or Fisher's exact test was employed to analyze categorical data. The Kaplan–Meier method and Log rank tests were used to evaluate and compare survival rates. Both univariate and multivariate analyses were conducted to analyze prognostic factors affecting survival. The albumin-bilirubin (ALBI) grade was classified refer to our previous study.[20] All analyzes were conducted with two-sided significance, $P < 0.05$ set as the significance threshold.

Results

Patients

A total of 221 eligible patients were enrolled, 103 and 118 of whom were treated with TACE-HAIC-LEN-PD-1i (THLP group) and TACE-LEN-PD-1i (TLP group), respectively. The mean follow-up was 23.8 ± 11.2 months in the THLP group and 18.4 ± 8.7 months in the TLP group. None of the patients was lost to follow-up. The patients' baseline characteristics were well-balanced and not statistically different between the two groups (P > 0.05). Ninety-two patients (89.3%) were male, and the mean age was 53.42 ± 10.85 years in the THLP group, while 101 patients (85.6%) were male, and the mean age was 53.23 ± 10.49 years in the TLP group. ECOG-PS score was 0 in 93.2% and 1 in 6.8% of patients in the THLP group vs. 0 in 95.8% and 1 in 4.2% of patients in the TLP group (P = 0.402). Child-Pugh class was A in 90.3% and B in 9.7% of patients in the THLP group vs. A in 92.4% and B in 7.6% of patients in the TLP group (P = 0.582). The mean largest tumor size was 9.86 ± 3.01 cm in the THLP group vs. 9.30 ± 3.25 cm in the TLP group (P = 0.186). Seventy-eight (75.7%) patients

in the THLP group vs. 83 (70.3%) patients in the TLP group had a tumor number of more than three, respectively (P = 0.369). For all enrolled patients, camrelizumab (30.8%), pembrolizumab (25.3%), toripalimab (18.6%), tislelizumab (16.3%), or sintilimab (9.0%) were administered, respectively. In the THLP group, there were 89 (86.4%), 35 (33.9%), 91 (88.3%), 16 (15.5%), and 22 (21.4%) patients that had received repeated TACE, ablation therapies, other MTTs or ICIs, ^{125}I seed implantation, and systemic chemotherapy as their second-line treatments, respectively. Whereas, in the TLP group, there were 57 (48.3%), 42 (35.6%), 38 (32.2%), 61 (51.7%), 46 (38.9%), and 30 (25.4%) patients that had received repeated TACE, HAIC, ablation therapies, other MTTs or ICIs, ^{125}I seed implantation, and systemic chemotherapy as their second-line treatments, respectively. The main patients' baseline characteristics are demonstrated in Table 1.

Table 1 Baseline Characteristics of the Patients

Characteristics	All patients (n = 221)	TACE-HAIC-LEN-PD-1i (n = 103)	TACE-LEN-PD-1i (n = 118)	*P*-value
Age (year)*	53.33 ± 10.67	53.42 ± 10.85	53.23 ± 10.49	0.895
≤60	168 (76.0)	81 (78.6)	87 (73.7)	
>60	53 (24.0)	22 (21.4)	31 (26.3)	
Gender				0.406
Female	28 (12.7)	11 (10.7)	17 (14.4)	
Male	193 (87.3)	92 (89.3)	101 (85.6)	
Hepatitis				0.544
Negative	13 (5.9)	5 (4.9)	8 (6.8)	
HBV/HCV	208 (94.1)	98 (95.1)	110 (93.2)	
ECOG PS				0.402
0	209 (94.6)	96 (93.2)	113 (95.8)	
1	12 (5.4)	7 (6.8)	5 (4.2)	
Child-Pugh class				0.582
A	202 (91.4)	93 (90.3)	109 (92.4)	
B	19 (8.6)	10 (9.7)	9 (7.6)	
ALBI grade				0.483
1	115 (52.0)	51 (49.5)	64 (54.2)	
2	106 (48.0)	52 (50.5)	54 (45.8)	
Maximum tumor diameter*	9.56 ± 3.15	9.86 ± 3.01	9.30 ± 3.25	0.186
5<TS≤10 cm	119 (53.8)	51 (49.5)	68 (57.6)	
TS>10 cm	102 (46.2)	52 (50.5)	50 (42.4)	
Number of tumors*				0.369
3	60 (27.1)	25 (24.3)	35 (29.7)	
>3	161 (72.9)	78 (75.7)	83 (70.3)	
AFP (ng/mL)*	26,488.9 ± 119,022.3	33,358.3 ± 159,756.8	18,619.1 ± 34,089.9	0.389
<400	125 (56.6)	53 (51.5)	72 (61.1)	
≥400	96 (43.4)	50 (48.5)	46 (38.9)	
PIVKA-II (mAU/mL)*	7505.3 ± 11,012.9	6201.7 ± 10,692.5	8677.2 ± 18,759.1	0.351
Albumin (g/dL)*	40.4 ± 3.6	40.6 ± 3.5	40.2 ± 3.7	0.474
Total bilirubin (mg/dL)*	17.1 ± 10.0	17.7 ± 11.8	16.6 ± 8.1	0.388
ALT (U/L)*	65.7 ± 49.8	70.4 ± 46.3	61.5 ± 52.6	0.187
AST (U/L)*	57.2 ± 47.9	59.7 ± 35.8	54.9 ± 56.6	0.469
Prothrombin time INR*	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.711
Platelet count (× 10^9/L)*	200.1 ± 87.6	207.9 ± 100.6	193.2 ± 74.3	0.213

Notes: Unless otherwise indicated, data are number of patients, with percentage in parentheses; *Data are means ± standard deviation.
Abbreviations: TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, programmed cell death protein-1 inhibitor; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; PS, performance score; ALBI, albumin–bilirubin; TS, tumor size; cm, centimeter; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

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Tumor Responses

The mRECIST criteria were used to assess tumor responses. In the whole cohort, for the best overall responses, the rates of CR, OR, and DC were 15.8%, 57.0%, and 84.6%, respectively (Table 2). Regarding the comparative analyses between the two groups, the rates of CR, OR, and DC were 22.3%, 70.8%, and 91.2%, respectively, in the THLP group vs. 10.2%, 44.9%, and 78.8%, respectively, in the TLP group ($P_{CR} = 0.014$, $P_{OR} < 0.001$, $P_{DC} = 0.011$) (Table 2 and Figure 2A). It indicated an obviously superior tumor response in the THLP group compared to that in the TLP group. Waterfall plots of the best overall responses showed that more than half of the patients achieved objective responses (Figure 2B).

Survival

At the end of the follow-up period, 151 patients had died. For the whole cohort patients, the median PFS (mPFS) was 9.5 (95% CI: 8.5–10.5) months, and the median OS (mOS) was 23.3 (95% CI: 21.7–24.9) months (Table 2). Twenty-one (20.4%) patients in the THLP group and 11 (9.3%) patients in the TLP group had sufficient tumor responses to receive conversion resection (P = 0.020) (Table 2). Furthermore, the responders (CR/PR) had better mPFS (11.5 vs. 5.5 months, P < 0.001) and mOS (30.2 vs. 17.5 months, P < 0.001) than the non-responders (SD/PD) (Figures 3A and B). The mPFS was statistically different between THLP group [11.0 (95% CI 10.2–11.8) months] and TLP group [8.0 (95% CI 6.9–9.1) months] (P < 0.001) (Table 2 and Figure 3C). Meanwhile, the mOS was 29.9 (95% CI: 24.9–34.9) months in the THLP group and 20.3 (95% CI: 18.1–22.5) months in the TLP group (P < 0.001) (Table 2 and Figure 3D). An obvious improvement of PFS and OS was noted, indicating that TACE-HAIC-LEN-PD-1i might have advantages over TACE-LEN-PD-1i. Further analyses revealed that the trends of superior PFS and OS were obtained by TACE-HAIC-LEN-PD-1i over TACE-LEN-PD-1i in all subgroups (Figures 4A and B). Stratified analyses by the five different types of PD-1i (camrelizumab group, n=68; pembrolizumab group, n=56; toripalimab group, n=41; tislelizumab group, n=36; and sintilimab group, n=20) indicated that, in each subgroup, the patients who underwent THLP had significantly superior mOS compared to those who received TLP (31.6 vs. 22.5 months, 32.8 vs. 21.7 months, 29.3 vs. 19.5 months, 27.5 vs. 20.8 months, and 28.5 vs. 18.6 months; all P values < 0.001). Similarly, the same trend was observed in mPFS (13.5 vs. 9.7 months, 12.9 vs. 8.0 months, 10.3 vs. 7.5 months, 9.8 vs. 6.5 months, and 11.7 vs. 7.9 months; all P values < 0.001).

Table 2 Clinical Efficacy

Efficacy	All Patients (n = 221)	TACE-HAIC-LEN-PD-1i (n = 103)	TACE-LEN-PD-1i (n = 118)	*P*-value*
Tumor responses				
mRECIST				
CR	35 (15.8)	23 (22.3)	12 (10.2)	0.014
PR	91 (41.2)	50 (48.5)	41 (34.7)	0.038
SD	61 (27.6)	21 (20.4)	40 (33.9)	0.025
PD	34 (15.4)	9 (8.8)	25 (21.2)	0.011
ORR (CR+ PR)	126 (57.0)	73 (70.8)	53 (44.9)	<0.001
DCR (CR+ PR+ SD)	187 (84.6)	94 (91.2)	93 (78.8)	0.011
Survival				
Progression-free survival†	9.5(8.5–10.5) months	11.0(10.2–11.8) months	8.0(6.9–9.1) months	<0.001
Overall survival†	23.3(21.7–24.9) months	29.9(24.9–34.9) months	20.3(18.1–22.5) months	<0.001
Conversion to surgical resection				0.020
With	32 (14.5)	21 (20.4)	11 (9.3)	
Without	189 (85.5)	82 (79.6)	107 (90.7)	

Notes: Unless otherwise indicated, data are number of patients, with percentage in parentheses; * TACE-HAIC-LEN-PD-1i vs.TACE-LEN-PD-1i; †Data are medians, with 95% confidence interval in parentheses.

Abbreviations: TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, programmed cell death protein-1 inhibitor; mRECIST: modify Response Evaluation Criteria in Solid Tumors; CR: complete response; PR: partial response; SD: stable disease; PD: progression disease; ORR: objective response rate; DCR: disease control rate.

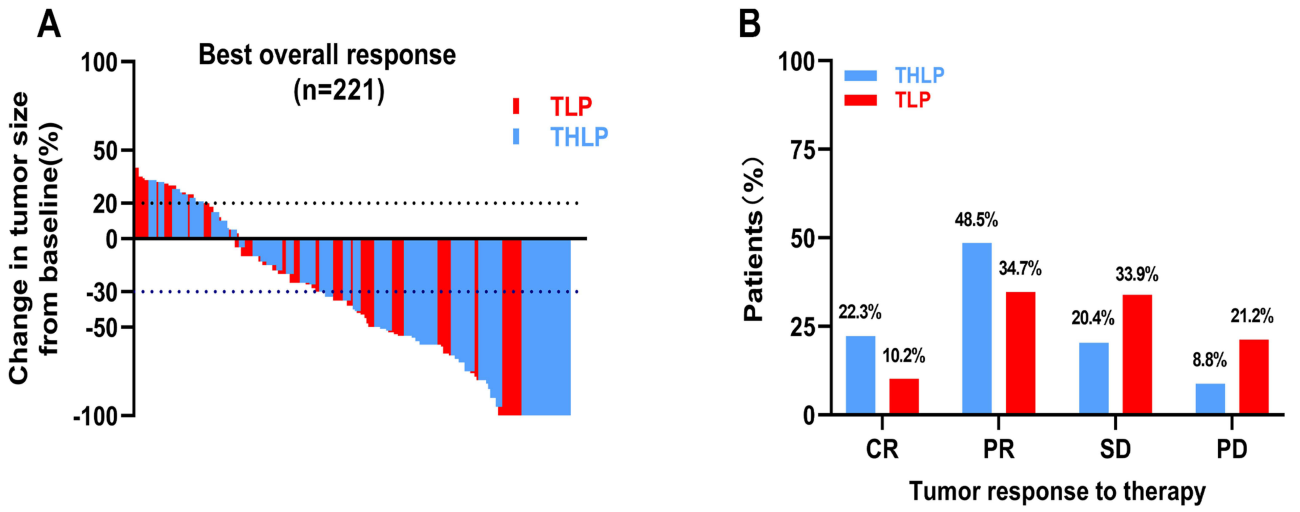

Figure 2 Tumor response assessment by mRECIST in patients receiving TLP and THLP. (**A**) Percent change from baseline in target lesion of the entire patient cohort; (**B**) Histogram depicting the tumor responses in the THLP and TLP groups.

Abbreviations: mRECIST, modify Response Evaluation Criteria in Solid Tumors; THLP, TACE-HAIC-LEN-PD-1i; TLP, TACE-LEN-PD-1; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, PD-1 inhibitor.

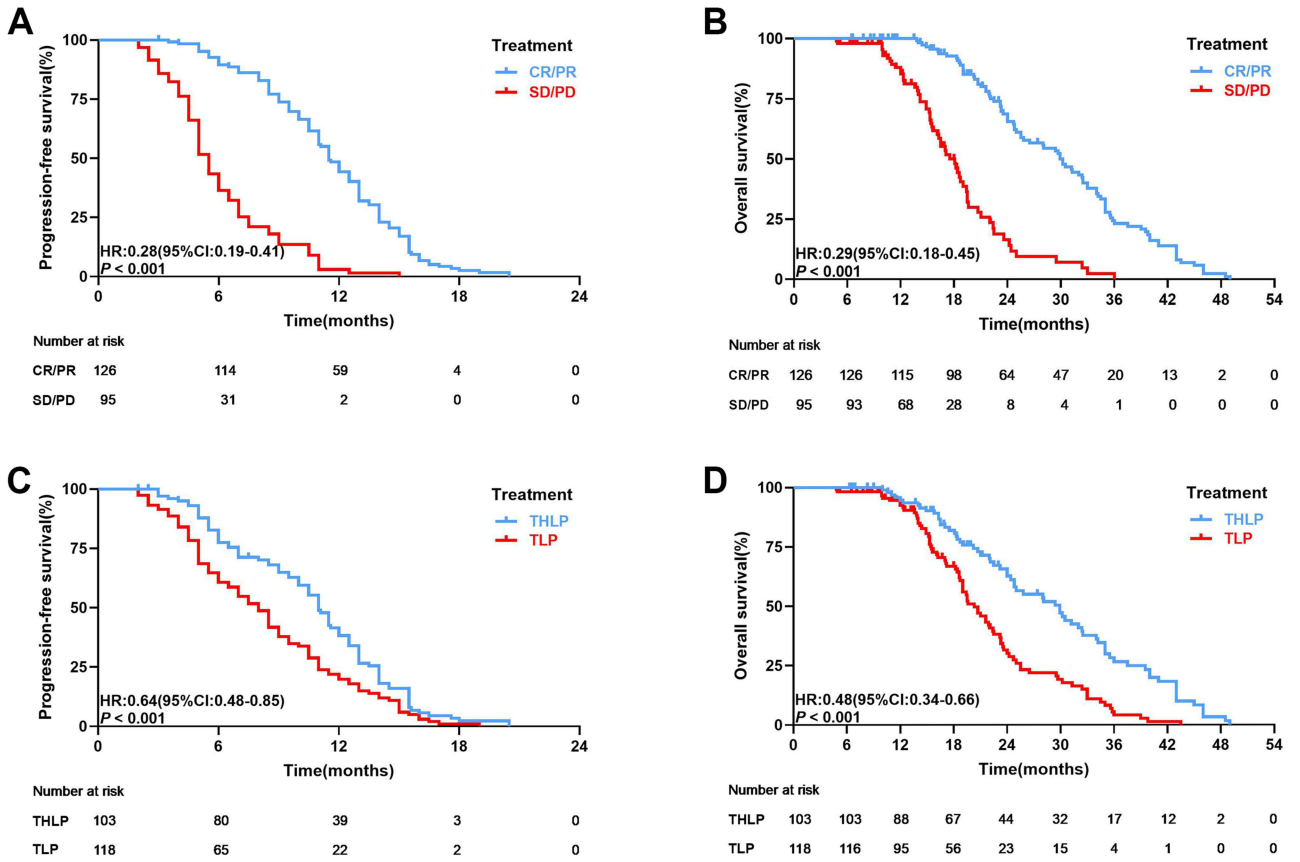

Figure 3 Kaplan-Meier survival curves for demonstrating patient survival. The PFS (**A**) and OS (**B**) in patients with tumor response (CR/PR vs SD/PD) according to mRECIST criteria. The PFS (**C**) and OS (**D**) in patients receiving THLP versus TLP.

Abbreviations: PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; mRECIST, modify Response Evaluation Criteria in Solid Tumors; THLP, TACE-HAIC-LEN-PD-1i; TLP, TACE-LEN-PD-1; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, PD-1 inhibitor.

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Prognostic Factors of Survival

Several key risk prognostic factors of OS were identified by the univariate analyses, including ECOG score greater than 0 (HR = 3.04, 95% CI 1.47–7.19, P < 0.001), advanced ALBI grade (HR = 3.20, 95% CI 1.97–5.62, P = 0.001), tumor size larger than 10 cm (HR = 6.59, 95% CI 2.10–9.64, P < 0.001), tumor number exceeding 3 (HR = 5.36, 95% CI 3.86–9.94, P < 0.001), alpha fetal protein (AFP) level ≥400 ng/mL (HR = 2.47, 95% CI 0.95–5.01, P = 0.024), without conversion resection (HR = 0.20, 95% CI 0.04–0.52, P < 0.001), and lack of HAIC treatment (HR = 0.32, 95% CI 0.19–0.61, P = 0.007) (Table 3). Further multivariate analyses revealed that ECOG score (P = 0.014), ALBI grade (P < 0.001), tumor size (P < 0.001), tumor number (P < 0.001), conversion resection (P < 0.001), and HAIC treatment (P < 0.001) were independent predictors of OS (Table 3).

Regarding PFS, univariate analyses indicated that tumor size larger than 10 cm (HR = 5.24, 95% CI 1.98–8.10, P < 0.001), tumor number exceeding 3 (HR = 3.12, 95% CI 1.25–6.07, P < 0.001), without conversion resection (HR = 0.11, 95% CI 0.06–0.49, P < 0.001), and lack of HAIC treatment (HR = 0.41, 95% CI 0.14–0.79, P = 0.021) obviously impacted PFS (Table 3). Following multivariate analyses confirmed that tumor size (P = 0.002), tumor number (P = 0.017), conversion resection (P = 0.039), and HAIC treatment were independent PFS predictors (P < 0.001) (Table 3).

Safety and Treatment Compliance

All TACE and HAIC procedures were successfully performed. Patients in the THLP group underwent a mean of 4.1 ± 1.5 TACE treatments, while patients in the TLP group underwent a mean of 6.3 ± 2.7 TACE treatments. The mean duration of LEN and PD-1i administration was 15.8 ± 3.1 months and 9.4 ± 2.3 months in the THLP group, respectively, and 13.9 ± 2.5 months and 7.7 ± 1.8 months in the THLP group, respectively. Additionally, patients in the THLP group received a mean of 3.6 ± 1.4 HAIC treatments.

Regarding interventional treatments, TACE-HAIC delay and TACE-HAIC discontinuation affected 28.2% and 9.7%, 31.4% and 7.6% of patients in the THLP and TLP groups, respectively. For patients in the THLP group, 27.2% of whom experienced interruptions in LEN administration, 17.5% had dose reductions, and 8.7% discontinued LEN. Meanwhile, for patients in the TLP group, 23.7% of whom experienced interruptions, 16.1% had dose reductions, and 9.3% discontinued LEN. Furthermore, 5.8% and 7.6% of patients discontinued PD-1i due to TRAEs in the THLP and TLP groups, respectively. In this study, no treatment-related mortality was noted, and all observed TRAEs were well tolerated and managed. According to the CTCAE 5.0, the incidence of any grade TRAEs (99.0% vs. 97.4%, P = 0.382) and grade 3–4 TRAEs (17.5% vs. 11.9%, P = 0.237) was not statistically different between the THLP and TLP groups. There were no grade 5 TRAEs among the whole patients. All TRAEs were summarized in Table 4.

Discussion

The prognosis of iHCC exhibits significant heterogeneity primarily due to diverse tumor characteristics. While TACE stands as the conventional therapeutic approach for iHCC, its long-term efficacy is hampered by elevated rates of tumor recurrence and metastasis.[21–23] Previous literatures have discussed the potential of combining locoregional and systemic therapies for iHCC, encompassing TACE, MTT, and immunotherapy.[7,8] To address the limitations of TACE, the combination of TACE with tyrosine kinase inhibitor (TKI) and PD-1i has emerged as a promising treatment modality for high tumor burden iHCC.[24–26] Nonetheless, the efficacy of HAIC for iHCC remains uncertain.

In this study, we administered either TACE-HAIC-LEN-PD-1i or TACE-LEN-PD-1i for patients with large iHCC. In real-world practice, TACE demonstrates a limited CR rate for high-burden HCC. Additionally, repeated sessions of TACE significantly impair liver function, which is a crucial prognostic factor for long-term OS. We hypothesized that incorporating HAIC could enhance the efficacy of TACE-LEN-PD-1i by improving the objective response rate (ORR) while mitigating the severe liver function damage associated with TACE. Consequently, in the TACE-HAIC-LEN-PD-1i group, we initially performed 2 to 3 cycles of TACE, followed by HAIC after each TACE cycle, and then proceeded with the standard administration of LEN-PD-1i. In contrast, the TACE-LEN-PD-1i group received only LEN-PD-1i following TACE. During follow-up or upon completion of study treatments, TACE was repeated “on demand” in cases of progressive disease.

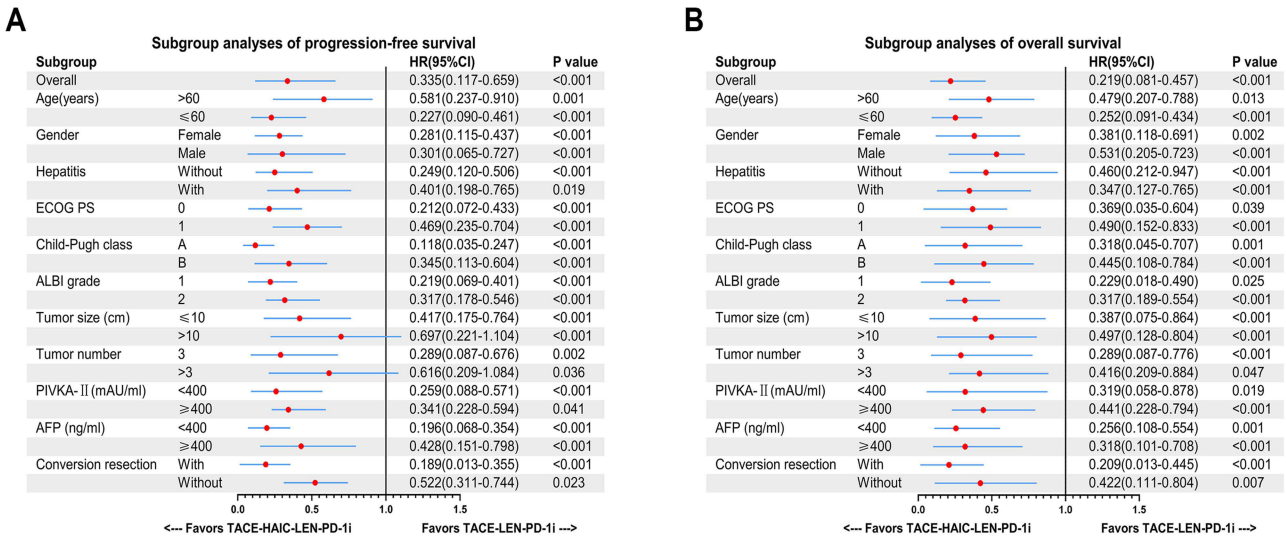

Figure 4 Subgroup analyses of progression-free survival (**A**) and overall survival (**B**).
Abbreviations: HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; cm, centimeter; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, PD-1 inhibitor.

Our data illustrated that TACE-HAIC-LEN-PD-1i was associated with a notable enhancement in terms of ORR, PFS, and OS for large iHCC compared to TACE-LEN-PD-1i. Further analysis demonstrated that patients associating with a complete or partial response had superior PFS and OS compared to those with stable disease or disease progression within the entire cohort. These findings suggest that addition of HAIC to TACE-LEN-PD-1i could ameliorate the prognosis of large iHCC by augmenting local tumor responses. Moreover, our observations indicated that TACE-HAIC-LEN-PD-1i was well-tolerated and safe, with no statistically significant difference in TRAEs compared to TACE-LEN-PD-1i. Lastly, prognostic assessments revealed that HAIC treatment independently predicted PFS and OS outcomes.

Table 3 Prognostic Factors of Progression-Free Survival and Overall Survival

Factor	Progression-Free Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ECOG score								
1 vs. 0	1.203(0.591–3.426)	0.339			3.035(1.469–7.192)	<0.001	1.517(0.875–3.801)	0.014
ALBI grade								
2 vs. 1	1.110(0.425–2.307)	0.162			3.201(1.965–5.621)	0.001	4.054(2.185–9.201)	<0.001
Tumor size (cm)								
>10 vs. 5-10	2.641(1.975–8.105)	<0.001	2.551(0.915–4.820)	0.002	3.591(2.101–9.644)	<0.001	3.310(0.435–8.101)	<0.001
Tumor number								
>3 vs. 3	3.116(1.251–6.067)	<0.001	1.954(1.071–5.782)	0.017	3.056(1.857–8.940)	<0.001	2.760(1.201–7.509)	<0.001
AFP (ng/mL)								
≥400 vs.<400	1.011(0.432–1.909)	0.803			2.471(0.951–6.011)	0.024	1.010(0.435–1.820)	0.158
Conversion resection								
With vs. Without	0.110(0.056–0.490)	<0.001	0.421(0.191–0.860)	0.039	0.201(0.039–0.517)	<0.001	0.051(0.018–0.196)	<0.001
HAIC treatment								
With vs. Without	0.407(0.135–0.787)	0.021	0.135(0.075–0.291)	<0.001	0.317(0.196–0.607)	0.007	0.121(0.036–0.344)	<0.001

Abbreviations: HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin–bilirubin; cm, centimeter; AFP, alpha-fetoprotein; HAIC, hepatic arterial infusion chemotherapy.

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Table 4 Treatment Related Adverse Events According to the CTCAE 5.0 Criteria

TRAEs	Any Grade			Grade 3–4		
	TACE-HAIC-LEN-PD-1i (n= 103)	TACE-LEN-PD-1i (n= 118)	*P*-value	TACE-HAIC-LEN-PD-1i (n= 103)	TACE-LEN-PD-1i (n=118)	*P*-value
Total	102 (99.0)	115 (97.4)	0.382	18 (17.5)	14 (11.9)	0.237
Nausea	91 (88.3)	96 (81.4)	0.151	0 (0)	0 (0)	/
Fatigue	83 (80.6)	88 (74.6)	0.287	0 (0)	0 (0)	/
Vomiting	67 (65.0)	53 (44.9)	0.003	0 (0)	0 (0)	/
Abdominal pain	80 (77.7)	82 (69.5)	0.170	6 (5.8)	8 (6.7)	0.771
Fever	50 (48.5)	48 (40.7)	0.240	0 (0)	0 (0)	/
Leukopenia/thrombopenia	48 (46.6)	36 (30.5)	0.014	0 (0)	0 (0)	/
Hand-foot syndrome	21 (20.4)	22 (18.6)	0.744	7 (6.8)	9 (7.6)	0.812
Diarrhea	19 (18.4)	17 (14.4)	0.417	9 (8.7)	7 (5.9)	0.422
Hypertension	14 (13.6)	11 (9.3)	0.317	10 (9.7)	8 (6.7)	0.427
Elevated bilirubin	23 (22.3)	18 (15.3)	0.177	8 (7.8)	7 (5.9)	0.589
Elevated ALT/AST	96 (93.2)	105 (88.9)	0.275	13 (12.6)	11 (9.3)	0.432
Decreased albumin	37 (35.9)	31 (26.3)	0.121	0 (0)	0 (0)	/
Ascites	10 (9.7)	8 (6.8)	0.427	0 (0)	0 (0)	/
Gastrointestinal hemorrhage	5 (4.9)	3 (2.5)	0.359	4 (3.9)	5 (4.2)	0.894
Hypothyroidism	8 (7.8)	5 (4.2)	0.266	0 (0)	0 (0)	/
Immune-mediated AEs	10 (9.7)	15 (12.7)	0.317	0 (0)	0 (0)	/

Note: Unless otherwise indicated, data are number of patients, with percentage in parentheses.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TRAEs, treatment related adverse events; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; LEN, lenvatinib; PD-1i, programmed cell death protein-1 inhibitors.

Achieving complete chemoembolization at the tumor microenvironment level of iHCC with high tumor burden poses challenges in clinical practice. Post-TACE hypoxia-induced tumor microenvironment promotes tumor-associated angiogenesis and immune evasion, recognized as critical factors in tumor progression.[27–29] TKIs are commonly utilized molecular targeted therapies known for their effective anti-tumor properties through angiogenesis inhibition within the hypoxic tumor microenvironment following TACE. LEN, a small-molecule TKI, demonstrates superior efficacy in normalizing tumor vasculature and achieving higher tumor response rates compared to sorafenib.[15] Clinical studies, such as the TACTICS-L trial, have shown that combining TACE with LEN (TACE-LEN) results in an ORR of 88.7% and an mPFS of 28.0 months in patients with unresectable iHCC.[30] Comparative analyses by Zhou et al have indicated significantly improved PFS and OS outcomes with TACE-LEN over TACE monotherapy for iHCC.[31] Additionally, studies by Shimose et al and Fu et al reported that LEN could serve as a salvage treatment option, prolonging PFS in patients with iHCC refractory to TACE and demonstrating superior ORR, PFS, and OS compared to TACE alone for HCC at BCLC stage B/C.[32,33]

ICIs have garnered increasing attention due to the recognition of the potential sensitivity of the HCC microenvironment to immunotherapy. While ICI monotherapy has not significantly extended OS because of a response rate of only about 15–20%, combination therapies such as TACE-TKI-ICI have been authorized for patients with uHCC.[34–36] Notably, LEN has shown consistent efficacy in enhancing T-cell infiltration in the tumor microenvironment, with PD-1i being widely recognized as commonly used ICIs for HCC.[37–39] The LEAP-012 study illustrated the superiority of TACE-LEN-PD-1i (pembrolizumab) over TACE monotherapy for iHCC not suitable for curative treatment in terms of PFS.[10] Moreover, Chen et al reported that TACE-LEN-PD-1i (Tislelizumab) yielded a more favorable prognosis in terms of PFS and OS compared to TACE-LEN for iHCC beyond the up-to-eleven criteria.[40] Furthermore, comparative analyses between TACE-LEN-PD-1i and TACE-LEN for uHCC (BCLC stage B/C HCC) have shown that TACE-LEN-PD-1i achieved superior ORR, PFS, and OS.

HAIC is a regional treatment option for HCC that offers advantages such as increased drug concentrations within the tumor, prolonged exposure of the tumor tissue to chemotherapeutic agents, and reduced systemic toxicity compared to traditional chemotherapy.[12–14] RCTs have confirmed the feasibility of HAIC regimens based on FOLFOX for advanced HCC.[12,13] In a study by Zhong et al, TACE-HAIC plus LEN (TACE-HAIC-LEN) was found to significantly improve ORR, PFS, and OS compared to TACE alone for HCC beyond the up-to-seven criteria.[41] Similarly, Lu et al reported that TACE-HAIC-LEN resulted in significantly prolonged PFS and OS compared to TACE combined with LEN (TACE-LEN) for patients with unresectable

massive HCC.[42] Furthermore, Cai et al demonstrated that adding HAIC to the TACE-LEN regimen markedly enhanced ORR and OS compared to TACE-LEN alone in patients with large HCC and major PVTT.[43]

Multiple studies have validated the feasibility of combining TACE-HAIC, atezolizumab, and bevacizumab for uHCC.[44–46] These studies have established a strong theoretical foundation for integrating TACE-HAIC, MTT, and ICIs for HCC treatment. However, the role of HAIC in the entire cohort of iHCC patients remains uncertain. In this investigation, we hypothesized that HAIC in combination with other therapies could elicit an anti-tumor response in non-responsive tumor tissues post-TACE. To enhance patient outcomes, we implemented a regimen involving TACE-HAIC-LEN-PD-1i for patients with unresectable iHCC and a substantial tumor burden (>5 cm). Our findings demonstrate that patients treated with TACE-HAIC-LEN-PD-1i exhibited obviously enhanced ORR, PFS, and OS in comparison with those receiving TACE-LEN-PD-1i. Thus, it suggested that the combined approach of TACE-HAIC-LEN-PD-1i holds promise as an effective therapeutic option for large iHCC.

In this investigation, all TRAEs were well tolerated and effectively managed, with no instances of treatment-related mortality. The most prevalent TRAEs included elevated levels of AST/ALT, nausea, fatigue, abdominal pain, vomiting, fever, leucopenia/thrombopenia, and decreased albumin, all of which were readily treatable. As per the CTCAE 5 criteria, no statistically significant difference in the occurrence of TRAEs of any grade or grade 3–4 between the groups receiving TACE-HAIC-LEN-PD-1i and TACE-LEN-PD-1i. Furthermore, no grade 5 TRAEs were reported. These findings were familiar to prior studies in this area.

To the best of our knowledge, this is the first study comparing TACE-HAIC-LEN-PD-1i with TACE-LEN-PD-1i in the entire cohort of iHCC patients. In addition, although this is a retrospective study, there is a sufficient sample size containing 221 patients with reliable statistical strength.

However, it is imperative to acknowledge potential limitations inherent in this analysis. First, despite the well-matched and comparable baseline characteristics of the two treatment cohorts, the entry criteria for patients undergoing TACE-HAIC-LEN-PD-1i or TACE-LEN-PD-1i were not formally established in each center, which may be a potential limitation. Second, although the utilization of various PD-1 inhibitors may be a limitation, these regimens are associated with similar mechanisms of anti-tumor and are recommended by several guidelines. Third, the predominant inclusion of hepatitis-related HCC cases necessitates further investigations stratified by distinct etiologies to corroborate these findings. Fourth, to mitigate severe chemotherapeutic-related treatment-emergent adverse events and account for heterogeneity between c-TACE and DEB-TACE, patients undergoing c-TACE were exclusively considered in this analysis. While previous studies have indicated comparable long-term outcomes between c-TACE and DEB-TACE for iHCC, exploring the feasibility of DEB-TACE-HAIC-LEN-PD-1i for extensive iHCC warrants future exploration.

Conclusions

TACE-HAIC-LEN-PD-1i was both safe and well-tolerated, providing superior clinical efficacy over TACE-LEN-PD-1i in patients with large iHCC. To validate the benefits of TACE-HAIC-LEN-PD-1i, RCTs are essential in the future, considering the limitations outlined above.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors (Jiayan Ni and Linfeng Xu) upon reasonable request.

Ethics Approval Statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Ethics Committee of the Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Approval No. SYSKY-2025-723-01).

Patient Consent Statement

Written informed consent was obtained before treatment.

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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 agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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