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The Efficacy and Safety of Bevacizumab Plus Anti-PD-1/PD-L1 Inhibitors in Combination with Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatocellular Carcinoma

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Objection: To report the efficacy and safety of triple combination therapy with bevacizumab plus anti-PD-1 (BP1) or anti-PD-L1 inhibitors (BPL) combined with hepatic arterial infusion chemotherapy (HAIC) as a first-line treatment for initially unresectable hepatocellular carcinoma (uHCC).

Methods: In this retrospective study, patients with initially uHCC received either BP1-HAIC or BPL-HAIC as first-line treatment. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate (ORR) and disease control rate (DCR).

Results: Between January 2020 and December 2022, a total of 136 patients with initially uHCC received triple combination therapy, with 76 in the BP1-HAIC group and 60 in the BPL-HAIC group. The median PFS for the entire cohort was 11.1 months (95% CI, 8.0–13.7 months), and the median OS was 22.4 months (95% CI, 21.3- not reached). Comparative analysis revealed no significant differences in PFS (HR, 0.91, $P = 0.69$) or OS (HR, 0.71, $P = 0.31$) between the BP1-HAIC and BPL-HAIC groups. The ORR was 46.3% per RECIST v1.1 and 66.9% per mRECIST, with a DCR of 83.1% under both criteria. Common adverse events (AEs) included hypoalbuminemia and elevated aspartate/alanine aminotransferase, with 5.1% (7/136) experienced upper gastrointestinal bleeding. Multivariate Cox analysis identified tumor number and BCLC stage as independent prognostic factors for OS, and tumor number for PFS.

Conclusion: Triple combination therapy demonstrated significant therapeutic efficacy and tumor response in initially uHCC. No notable differences in outcomes were observed between the BP1-HAIC and BPL-HAIC groups. AEs were manageable in clinical practice.

Keywords: hepatocellular carcinoma, immune checkpoint inhibitor, bevacizumab, hepatic arterial infusion chemotherapy, adverse event

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide with high incidence and mortality rates over the past decade.[1,2] Recently, a significant progress has been made in the treatment of patients with HCC.[3,4] Bevacizumab, a VEGF monoclonal antibody, combined with anti-PD-L1 or anti-PD-1 immunotherapies, is effective in the treatment of unresectable HCC (uHCC).[5–7] Specifically, bevacizumab plus atezolizumab, an anti-PD-L1 inhibitor, has been endorsed by multiple national and global clinical guidelines as a first-line treatment for uHCC and has demonstrated significant improvements in overall survival (OS) compared to sorafenib in the Phase III IMbrave150 trial.[8,9] Similarly,

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the ORIENT-32 trial demonstrated the efficacy of sintilimab, an anti-PD-1 inhibitor, plus a bevacizumab biosimilar (IBI305), which led to its approval in China as first-line therapy for uHCC.[10]

However, despite these advancements in treatment, the clinical management of uHCC remains challenging owing to great variations in survival rates between tumors with similar characteristics and stages. Recently, the combination of atezolizumab plus bevacizumab or sintilimab plus bevacizumab biosimilar has become the first-line treatment for uHCC instead of sorafenib. A comparative study showed that combining systemic therapy with hepatic arterial infusion chemotherapy (HAIC) can enhance the efficacy of anti-HCC treatments.[11] HAIC, which could continuous and repeated delivery of chemotherapeutic drugs into the tumor feeding artery, have shown potent antitumor efficacy when compared to sorafenib for advanced HCC.[12,13] In addition, a phase III trial found that HAIC using oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX-HAIC) significantly improved overall survival compared to TACE in patients with large uHCC.[14] Furthermore, it has also been suggested that combining sorafenib with HAIC may provide greater benefits for patients with advanced hepatocellular carcinoma than sorafenib alone.[15] Multiple Asian guidelines, including the Chinese, Taiwanese, and Korean guidelines, have recommended HAIC as a treatment option in patients with uHCC.[16,17] Considering the different anti-tumor mechanisms of bevacizumab, anti-PD-1/PD-L1 inhibitors, and HAIC, the combination of these three modalities may show potential synergistic effects and promising preliminary efficacy results in uHCC.

Whether the triple combination therapy improves overall survival (OS) in patients with uHCC remains uncertain.[18,19] Herein, we conducted a real-world study to assess the safety and efficacy of the triple combination of bevacizumab plus anti-PD-1/PD-L1 inhibitors and HAIC as a first-line treatment for uHCC and explored potential prognostic factors.

Methods

Study Design and Participants

This real-world study retrospectively collected the electronic medical record data from patients with initially uHCC at the Sun Yat-sen University Cancer Center who received triple combination therapy. Participants who received bevacizumab plus anti-PD-1 inhibitor (BP1) or bevacizumab plus anti-PD-L1 inhibitor (BPL) from January 2020 to December 2022 were screened. The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of the Sun Yat-sen University Cancer Center (IRB: B2022-200-01).

Inclusion criteria were: (1) had no history of previous therapy for HCC; (2) combined with HAIC treatment; (3) diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) criteria.[20] The exclusion criteria were as follows: (1) lack of baseline radiological examination or failure to complete the first review; (2) absence of measurable lesions; (3) presence of other invasive malignancies.

Procedures

Bevacizumab and anti-PD-1/PD-L1 inhibitors were administered every 3–4 weeks, one day before or after the HAIC procedure. Anti-PD-1 antibodies, including sintilimab (200 mg), tislelizumab (200 mg), and toripalimab (240 mg), were intravenously administered according to its instructions. Atezolizumab, an anti-PD-L1 inhibitor, was administered at a dose of 1200 mg. Bevacizumab was administered intravenously, ensuring a minimum interval of 5 min from the prior drug, at a dose of 15 mg/kg. Bevacizumab and anti-PD-1/PD-L1 inhibitors may be transiently or permanently discontinued in cases of grade 3–4 Adverse events (AEs) such as hypertension, elevated AST, upper gastrointestinal bleeding, and any other grade 3 or 4 treatment-related toxicity.

HAIC with oxaliplatin, 5-fluorouracil, and leucovorin (HAIC-FOLFOX) was performed as previously described.[12,13,15] The HAIC-FOLFOX procedure was as follows: the femoral artery was punctured using the Seldinger technique, and digital subtraction angiography was performed to determine the main feeding arteries of the tumor. Subsequently, the microcatheter was placed at the main feeding arteries of the tumor, and HAIC-FOLFOX chemotherapeutic agents were sequentially infused within 2 days: oxaliplatin at 85 mg/m^2 from hour 0 to 2 on day 1, leucovorin 400 mg/m^2 from hour 2 to 3 on day 1, 5-fluorouracil 400 mg/m^2 bolus at hour 3, and 2400 mg/m^2 over 23h on days 1 and 2. The dose reduction and discontinuation of HAIC were based on previous clinical trials.[21] Specifically, if patients experienced grade 3 or 4 AEs such as severe diarrhea, skin toxicity, stomatitis, or any other grade 3 or 4 major organ drug-related toxicity, the dose of

5-fluorouracil was reduced to 300mg/m^2 per cycle bolus and 1800mg/m^2 per cycle continuous infusion. For oxaliplatin, the dose was adjusted to 65 mg/m^2 per cycle in the event of grade 3 or 4 thrombocytopenia, neutropenia, or any other grade 3 or 4 major organ drug-related toxicities.

Outcome Assessment

The primary endpoint was PFS, defined as the time from the initiation of triple combination therapy to the date of disease progression or death, evaluated using the RECIST v1.1 criteria and mRECIST criteria.[22,23] The secondary endpoints were OS, defined as the time from the initiation of triple combination therapy to death from any cause; ORR, defined as the proportion of patients with complete response (CR) or partial response (PR); and disease control rate (DCR), defined as the proportion of patients with complete response, partial response, or stable disease.

The routine follow-up intervals were 6–8 weeks. Enhanced Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) were performed to evaluate treatment responses. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0).

Statistical Analysis

Categorical variables are presented as numbers and percentages. The Kaplan–Meier method was used to estimate the OS and PFS. The Log rank test was used to analyze the differences in OS and PFS among subgroups. Univariate and multivariate analyses were performed using a Cox proportional hazards model to identify the prognostic factors potentially associated with OS and PFS. All statistical analyses were performed using R software version 4.2.2.

Results

Patient Characteristics

A total of 671 liver cancer patients who received bevacizumab plus anti-PD-1/PD-L1 inhibitors were initially screened at the Sun Yat-sen University Cancer Center between January 2020 and December 2022. Exclusions were made for patients who had received prior anti-cancer treatment (n = 477), did not receive combined HAIC treatment (n = 15), were diagnosed with conditions other than HCC (n = 9), lacked baseline radiological examinations (n = 11), had no measurable lesions (n = 3), or failed to complete the first review (n = 20). Finally, 136 patients who received either BP1-HAIC or BPL-HAIC as first-line treatment for HCC were included in this analysis. Specifically, 76 patients were treated with BP1-HAIC, and 60 patients were treated with BPL-HAIC (Figure 1). Among the patients who received BP1-HAIC treatment, the vast majority of anti-PD-1 inhibitors was sintilimab (74/76), while the remaining two cases used tislelizumab (1/76) and toripalimab (1/76), respectively.

Across all patients, 89 (65.4%) were diagnosed with BCLC stage C, and 117 (86.0%) were infected with HBV. Additionally, 73 (53.7%) had a tumor size > 10 cm, 74 (54.4%) exhibited portal vein tumor thrombosis (PVTT), and 42 (30.9%) had extrahepatic metastasis. Notably, 124 patients (91.2%) were beyond the up-to-seven criteria. There were no significant differences between the treatment groups (Table 1).

Radiologic Response Rate

In the BP1-HAIC group, 76 patients were treated with 338 cycles of bevacizumab plus anti-PD-1 inhibitor (median, 3) and 260 cycles of HAIC (median, 4). In the BPL-HAIC group, 60 patients were treated with 307 cycles of bevacizumab plus anti-PD-L1 inhibitor (median, 4) and 223 cycles of HAIC (median, 4). Among all patients, 1 patient (0.7%) achieved CR, 62 patients (45.6%) achieved PR, 50 participants (36.8%) achieved SD, and 23 patients (16.9%) achieved PD. The tumor responses based on RECIST v1.1 and mRECIST are shown in Table 2. The ORR was 46.3% for RECIST v1.1, 66.9% for mRECIST, and the DCR was 83.1% for both RECIST v1.1, and mRECIST. In addition, no statistically significant difference was observed in the ORR and DCR between the BP1-HAIC and BPL-HAIC groups.

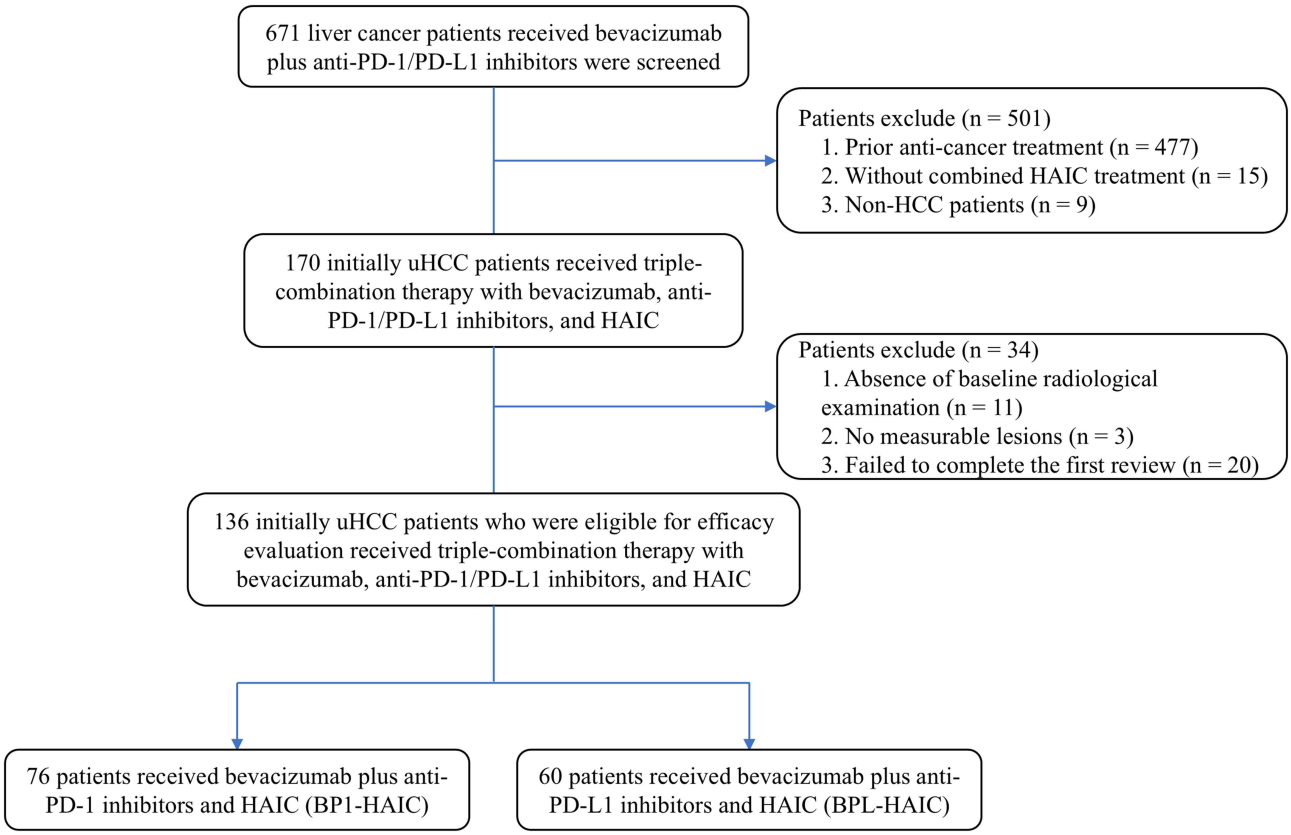

Figure 1 Patient selection flow.
Abbreviations: uHCC, unresectable hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; BP1, bevacizumab plus anti-PD-1 inhibitor; BPL, bevacizumab plus anti-PD-L1 inhibitor.

PFS and OS Analysis

The median follow-up was 16.1 months (95% CI, 15.5–17 months). In the entire study cohort, the median PFS was 11.1 months (95% CI, 8–13.7 months) and the median OS was 22.4 months (95% CI, 21.3-not reached). The 6-, 12-, and 18-month OS rates were 90.1%, 79.6%, and 67.4%, respectively. After triple combination therapy, 19 patients (14.0%) achieved disease downstaging and underwent curative resection (9 patients in the BP1-HAIC group and 9 patients in the BPL-HAIC group) or

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Overall (n = 136)	BP1-HAIC (n = 76)	BPL-HAIC (n = 60)	p-value
Age				0.21
≤ 60	109 (80.1%)	58 (76.3%)	51 (85.0%)	
> 60	27 (19.9%)	18 (23.7%)	9 (15.0%)	
Sex				0.47
Male	128 (94.1%)	70 (92.1%)	58 (96.7%)	
Female	8 (5.9%)	6 (7.9%)	2 (3.3%)	
AFP				> 0.99
≤ 400	59 (43.4%)	33 (43.4%)	26 (43.3%)	
> 400	77 (56.6%)	43 (56.6%)	34 (56.7%)	
PIVKA				> 0.99
≤ 40	8 (5.9%)	5 (6.6%)	3 (5.0%)	
> 40	128 (94.1%)	71 (93.4%)	57 (95.0%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n = 136)	BP1-HAIC (n = 76)	BPL-HAIC (n = 60)	p-value
ALB				0.090
≤ 40	42 (30.9%)	28 (36.8%)	14 (23.3%)	
> 40	94 (69.1%)	48 (63.2%)	46 (76.7%)	
TBIL				0.81
≤ 20.5	96 (70.6%)	53 (69.7%)	43 (71.7%)	
> 20.5	40 (29.4%)	23 (30.3%)	17 (28.3%)	
Child-Pugh				0.32
A	132 (97.1%)	75 (98.7%)	57 (95.0%)	
B	4 (2.9%)	1 (1.3%)	3 (5.0%)	
ALBI				0.23
1	90 (66.2%)	47 (61.8%)	43 (71.7%)	
2	46 (33.8%)	29 (38.2%)	17 (28.3%)	
Hepatitis B infection				0.85
No	19 (14.0%)	11 (14.5%)	8 (13.3%)	
Yes	117 (86.0%)	65 (85.5%)	52 (86.7%)	
ALT				0.25
≤ 50	81 (59.6%)	42 (55.3%)	39 (65.0%)	
> 50	55 (40.4%)	34 (44.7%)	21 (35.0%)	
AST				0.86
≤ 40	35 (25.7%)	20 (26.3%)	15 (25.0%)	
> 40	101 (74.3%)	56 (73.7%)	45 (75.0%)	
Tumor size (cm)				0.19
≤ 10	63 (46.3%)	39 (51.3%)	24 (40.0%)	
> 10	73 (53.7%)	37 (48.7%)	36 (60.0%)	
Tumor number				0.67
≤ 3	48 (35.3%)	28 (36.8%)	20 (33.3%)	
> 3	88 (64.7%)	48 (63.2%)	40 (66.7%)	
Up to 7 criteria				0.67
Within	12 (8.8%)	6 (7.9%)	6 (10.0%)	
Outside	124 (91.2%)	70 (92.1%)	54 (90.0%)	
PVTT				0.64
Absent	62 (45.6%)	36 (47.4%)	26 (43.3%)	
Present	74 (54.4%)	40 (52.6%)	34 (56.7%)	
Extra-hepatic metastasis				0.84
Absent	94 (69.1%)	52 (68.4%)	42 (70.0%)	
Present	42 (30.9%)	24 (31.6%)	18 (30.0%)	
BCLC stage				0.53
BCLC A	16 (11.8%)	9 (11.8%)	7 (11.7%)	
BCLC B	31 (22.8%)	19 (25.0%)	12 (20.0%)	
BCLC C	89 (65.4%)	48 (63.2%)	41 (68.3%)	

Abbreviations: BP1-HAIC, bevacizumab plus anti-PD-1 inhibitor and hepatic arterial infusion chemotherapy; BPL-HAIC, bevacizumab plus anti-PD-L1 inhibitor and hepatic arterial infusion chemotherapy; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; ALB, albumin; TBIL, total bilirubin; ALBI, albumin-bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase, PVTT, portal vein tumor thrombosis; BCLC stage, The Barcelona Clinic Liver Cancer Staging System.

ablation (1 patient in the BP1-HAIC group). Furthermore, Comparative analysis revealed no significant differences in OS (BPL-HAIC versus BP1-HAIC, 22.4 months vs not reached; HR, 1.40; $P = 0.31$) and PFS (BPL-HAIC versus BP1-HAIC, 10.3 vs 11.9 months; HR, 1.10; $P = 0.69$) between the BPL-HAIC and BP1-HAIC groups (Figure 2).

Multivariate analysis was shown in Table 3 and revealed that tumor number was an independent prognostic factor for PFS (tumor number > 3 vs tumor number ≤ 3; HR, 1.95 (95% CI, 1.15–3.30); $P = 0.013$). There were significances for

Table 2 Tumor Response Rate in Different Groups

	RECIST V1.1			mRECIST		
	Overall (n = 136)	BP1-HAIC (n = 76)	BPL-HAIC (n = 60)	Overall (n = 136)	BP1-HAIC (n = 76)	BPL-HAIC (n = 60)
Complete response, n (%)	1 (0.7%)	1 (1.3%)	0	20 (14.7%)	9 (11.8%)	11 (18.3%)
Partial response, n (%)	62 (45.6%)	31 (40.8%)	31 (51.7%)	71 (52.2%)	41 (53.9%)	30 (50.0%)
Stable disease, n (%)	50 (36.8%)	30 (39.5%)	20 (33.3%)	22 (16.2%)	12 (15.8%)	10 (16.7%)
Progressive disease, n (%)	23 (16.9%)	14 (18.4%)	9 (15.0%)	23 (16.9%)	14 (18.4%)	9 (15.0%)
ORR, n (%)	63 (46.3%)	32 (42.1%)	31 (51.7%)	91 (66.9%)	50 (65.7%)	41 (68.3%)
Disease control rate, n (%)	113 (83.1%)	62 (81.6%)	51 (85%)	113 (83.1%)	62 (81.6%)	51 (85.0%)

Abbreviations: RECIST V1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; DCR, disease control rate; BP1-HAIC, bevacizumab plus anti-PD-1 inhibitor and hepatic arterial infusion chemotherapy; BPL-HAIC, bevacizumab plus anti-PD-L1 inhibitor and hepatic arterial infusion chemotherapy.

the association between OS and tumor number (tumor number > 3 vs tumor number ≤ 3; HR, 3.33 (95% CI, 1.34–8.26); $P = 0.009$) and BCLC stage (BCLC C vs BCLC A/B; HR, 6.55 (95% CI, 1.50–28.53); $P = 0.012$) (Figure 3).

Safety and Tolerability

No treatment-related deaths were observed in this study; the frequency of treatment-related AEs is shown in Table 4. The most common treatment-related AEs included hypoalbuminemia (83.8%), elevated aspartate transaminase (AST) (81.6%), and elevated alanine transaminase (ALT) (66.2%). The most frequent grade 3–4 treatment related AEs were elevated AST (34.6%), hypertension (13.2%), and elevated ALT (12.5%). None of the patients required hospitalization owing to severe liver function deterioration or treatment-related toxicities. Liver dysfunction, such as elevated AST, elevated ALT, hypoalbuminemia, and hyperbilirubinemia, was mainly mild to moderate and resolved within a week

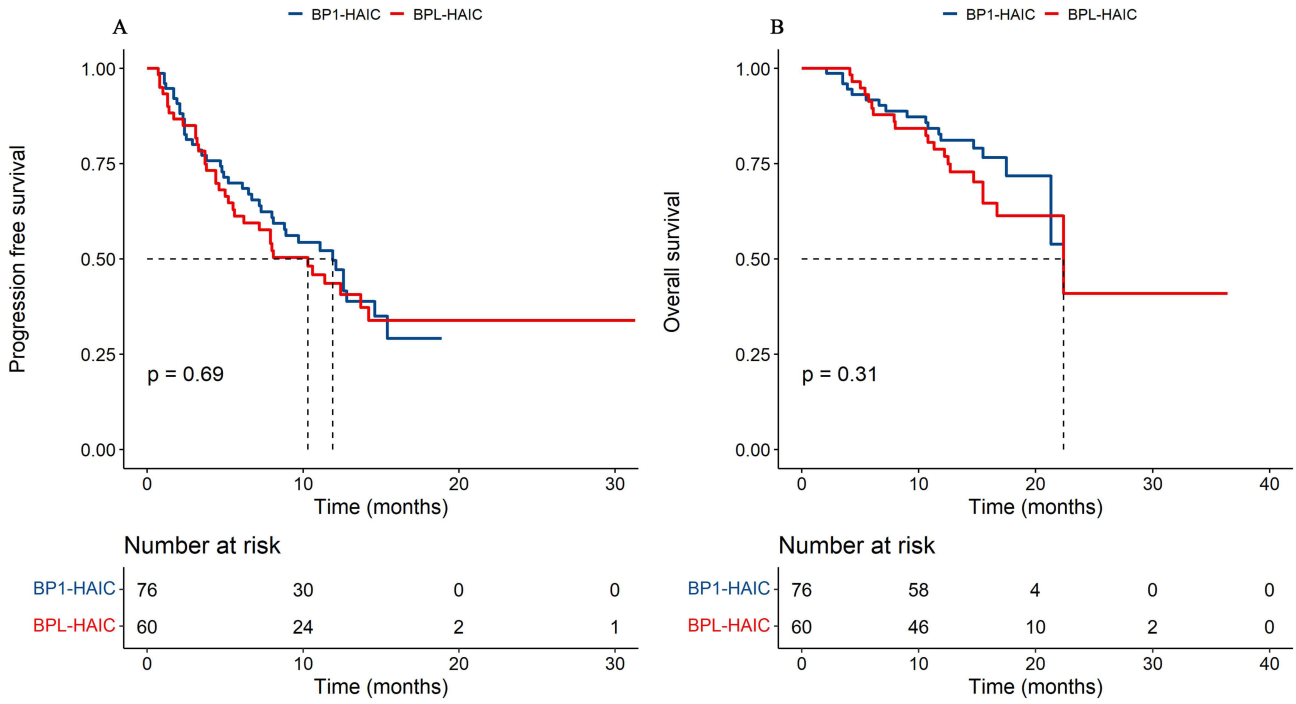

Figure 2 Kaplan-Meier analysis of overall and progression-free survival. Kaplan-Meier estimate of progression-free survival (**A**) and overall survival (**B**) in the BP1-HAIC group (n = 76) and BPL-HAIC group (n = 60).
Abbreviations: BP1-HAIC, bevacizumab plus anti-PD-1 inhibitor and hepatic arterial infusion chemotherapy; BPL-HAIC, bevacizumab plus anti-PD-L1 inhibitor and hepatic arterial infusion chemotherapy.

Table 3 Univariate and Multivariate Analysis for OS and PFS

		Overall Survival		Progression Free Survival	
		Univariate Analysis HR (95% CI)	**Multivariate Analysis HR (95% CI)**	**Univariate Analysis HR (95% CI)**	**Multivariate Analysis HR (95% CI)**
Treatment	BP1-HAIC	–	–	–	–
	BPL-HAIC	1.40 (0.73–2.68, p = 0.31)	–	1.10 (0.70–1.73, p = 0.69)	–
Age	≤ 60	–	–	–	–
	> 60	0.90 (0.40–2.05, p = 0.79)	–	0.68 (0.37–1.27, p = 0.23)	–
Sex	Male	–	–	–	–
	Female	1.75 (0.62–4.97, p = 0.29)	–	0.72 (0.26–1.98, p = 0.53)	–
AFP	≤ 400	–	–	–	–
	> 400	1.82 (0.92–3.58, p = 0.085)	–	1.60 (1.00–2.55, p = 0.051)	–
PIVKA	≤ 40	–	–	–	–
	> 40	2.61 (0.36–19.09, p = 0.34)	–	1.34 (0.49–3.68, p = 0.57)	–
ALB	≤ 40	–	–	–	–
	> 40	0.38 (0.20–0.72, p = 0.003)	0.61 (0.19–1.96, p = 0.40)	0.69 (0.43–1.10, p = 0.12)	–
TBIL	≤ 20.5	–	–	–	–
	> 20.5	2.13 (1.10–4.15, p = 0.025)	1.65 (0.76–3.57, p = 0.20)	1.30 (0.80–2.12, p=0.29)	–
Child-Pugh	A	–	–	–	–
	B	0.85 (0.12–6.20, p = 0.87)	–	1.40 (0.44–4.46, p = 0.57)	–
ALBI	1	–	–	–	–
	2	2.41 (1.26–4.60, p = 0.008)	1.08 (0.32–3.70, p = 0.90)	1.47 (0.92–2.34, p = 0.11)	–
Hepatitis B infection	No	–	–	–	–
	Yes	0.77 (0.34–1.75, p = 0.53)	–	1.67 (0.80–3.48, p = 0.17)	–
ALT	≤ 50	–	–	–	–
	> 50	1.21 (0.63–2.33, p = 0.56)	–	1.28 (0.81–2.01, p = 0.30)	–
AST	≤ 40	–	–	–	–
	> 40	5.98 (1.80–19.84, p = 0.003)	3.43 (0.95–12.37, p = 0.060)	2.58 (1.36–4.89, p = 0.004)	1.93 (0.97–3.86, p = 0.063)
Tumor size	≤ 10	–	–	–	–
	> 10	2.36 (1.18–4.72, p = 0.015)	1.94 (0.91–4.13, p = 0.087)	1.59 (1.00–2.53, p = 0.048)	1.44 (0.87–2.39, p = 0.15)
Tumor number	≤ 3	–	–	–	–
	> 3	2.95 (1.33–6.52, p = 0.008)	3.33 (1.34–8.26, p = 0.009)	2.19 (1.30–3.69, p = 0.003)	1.95 (1.15–3.30, p = 0.013)
PVTT	Absent	–	–	–	–
	Present	2.23 (1.12–4.44, p = 0.023)	0.55 (0.19–1.58, p = 0.27)	1.94 (1.21–3.12, p = 0.006)	1.09 (0.51–2.31, p = 0.83)
Extrahepatic metastasis	Absent	–	–	–	–
	PRESENT	2.53 (1.32–4.84, p = 0.005)	0.60 (0.24–1.47, p = 0.26)	2.22 (1.40–3.52, p ≤ 0.001)	1.11 (0.60–2.04, p = 0.74)
BCLC stage	BCLC A/B	–	–	–	–
	BCLC C	4.49 (1.75–11.55, p = 0.002)	6.55 (1.50–28.53, p = 0.012)	2.63 (1.53–4.53, p ≤ 0.001)	2.11 (0.79–5.64, p = 0.14)

Abbreviations: BP1-HAIC, bevacizumab plus anti-PD-1 inhibitor and hepatic arterial infusion chemotherapy; BPL-HAIC, bevacizumab plus anti-PD-L1 inhibitor and hepatic arterial infusion chemotherapy; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; ALB, albumin; TBIL, total bilirubin; ALBI, albumin-bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; PVTT, portal vein tumor thrombosis; BCLC stage, The Barcelona Clinic Liver Cancer Staging System.

following symptomatic treatment. Notably, 7 patients (5.1%) experienced upper gastrointestinal bleeding, with 4 patients (2.9%) suffering severe (grade ≥ 3) bleeding. Two patients (one in the BP1-HAIC group and one in the BPL-HAIC group) underwent TIPS to prevent variceal rebleeding. One patient in the BP1-HAIC group underwent endoscopic hemostasis, and one patient in the BPL-HAIC group received symptomatic treatment and was discharged. The overall incidence of AEs was comparable between the BP1-HAIC and BPL-HAIC groups.

Discussion

This study contributes to the growing body of evidence by assessing the real-world efficacy and safety of triple combination therapy with bevacizumab, anti-PD-1/PD-L1 inhibitors, and HAIC for the treatment of uHCC in routine clinical practice. In this real-world study, ether BP1-HAIC or BPL-HAIC showed a promising anti-tumor effect and no significant difference in mPFS and mOS. Furthermore, the treatment related AEs was tolerable.

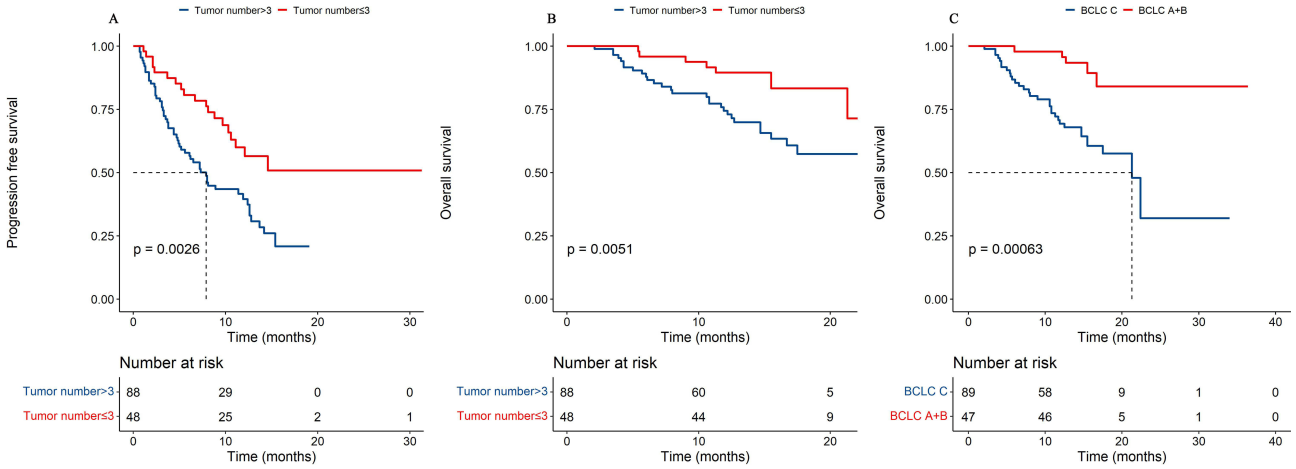

Figure 3 Kaplan-Meier analysis of overall and progression-free survival in subgroups. Kaplan-Meier estimate of progression-free survival (**A**) and overall survival (**B**) in the tumor number > 3 group (n = 88) and tumor number ≤ 3 group (n = 48). (**C**) Kaplan-Meier estimate of overall survival in the BCLC stage C group (n = 89) and BCLC stage A/B group (n = 47). BCLC, Barcelona Clinic Liver Cancer staging.

A recent update from the IMbrave150 trial demonstrated that the combination of atezolizumab and bevacizumab achieved an ORR of 30% and a median PFS spanning 6.9 months for uHCC.[24] Similarly, the ORIENT-32 trial revealed that sintilimab plus bevacizumab biosimilar (IBI305) yielded an ORR of 21% and a median PFS of 4.6 months in uHCC patients. Intriguingly, our study results showed that the triple combination therapy produced an ORR of 46.3% and a median PFS of 11.1 months, suggesting that the addition of HAIC further enhanced the efficacy of systemic therapy. This improvement may be attributed to bevacizumab's ability to transiently normalize vascular structure and function, reducing tumor hypoxia and acidosis, and thereby enhancing immune cell infiltrating. This vascular normalization

Table 4 Treatment-Related Adverse Events

Adverse Events, n (%)	Overall (n = 136)		BP1-HAIC (n = 76)		BPL-HAIC (n = 60)	
	Any grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Leukopenia	24(17.6%)	4(2.9%)	12(15.8%)	2(2.6%)	12(20.0%)	2(3.3%)
Decreased neutrophil count	35(25.7%)	11(8.1%)	21(27.6%)	6(7.9%)	14(23.3%)	5(8.3%)
Anaemia	67(49.3%)	2(1.5%)	39(51.3%)	1(1.3%)	28(46.7%)	1(1.7%)
Platelet count decrease	43(31.6%)	7(5.1%)	22(28.9%)	5(6.6%)	21(35.0%)	2(3.3%)
Alanine aminotransferase increase	90(66.2%)	17(12.5%)	50(65.8%)	7(9.2%)	40(66.7%)	10(16.7%)
Aspartate aminotransferase increase	111(81.6%)	47(34.6%)	65(85.5%)	28(36.8%)	46(76.7%)	19(31.7%)
Hyperbilirubinemia	69(50.7%)	12(8.8%)	33(43.4%)	7(9.2%)	36(60.0%)	5(8.3%)
Hypoalbuminemia	114(83.8%)	0	65(85.5%)	0	49(81.7%)	0
Hypothyroidism	22(16.2%)	0	11(14.5%)	0	11(18.3%)	0
Proteinuria	48(35.3%)	7(5.1%)	34(44.7%)	4(5.3%)	14(23.3%)	3(5.0%)
Hypertension	44(32.4%)	18(13.2%)	22(28.9%)	10(13.2%)	22(36.7%)	8(13.3%)
Fatigue	75(55.1%)	3(2.2%)	43(56.6%)	2(2.6%)	32(53.3%)	1(1.7%)
Decreased weight	52(38.2%)	1(0.7%)	23(30.3%)	1(1.3%)	29(48.3%)	0
Abdominal pain	46(33.8%)	2(1.5%)	24(31.6%)	1(1.3%)	22(36.7%)	1(1.7%)
Diarrhea	23(16.9%)	3(2.2%)	16(21.1%)	2(2.6%)	7(11.7%)	1(1.7%)
Nausea	58(42.6%)	0	30(39.5%)	0	28(46.7%)	0
Vomiting	40(29.4%)	1(0.7%)	24(31.6%)	1(1.3%)	13(21.7%)	0
Hand–foot skin reaction	3(2.2%)	0	2(2.6%)	0	1(1.7%)	0
Rash	5(3.7%)	0	2(2.6%)	0	3(5.0%)	0
Upper gastrointestinal haemorrhage	7(5.1%)	4(2.9%)	3(3.9%)	2(2.6%)	4(6.7%)	2(3.3%)

Abbreviations: BP1-HAIC, bevacizumab plus anti-PD-1 inhibitor and hepatic arterial infusion chemotherapy; BPL-HAIC, bevacizumab plus anti-PD-L1 inhibitor and hepatic arterial infusion chemotherapy.

facilitates the delivery of chemotherapeutic agents via HAIC, which induces tumor cell death and promotes the release of tumor antigens. These neoantigens increase tumor immunogenicity by activating $CD8^+$ cytotoxic T cells, ultimately enhancing antitumor activity. A Phase II trial has demonstrated that the combination of HAIC with sintilimab and a bevacizumab biosimilar yielded an ORR of 58.6% in treating uHCC.[25] Moreover, The LetoHAIC study further demonstrated an elevated ORR of 67.6% in advanced HCC patients treated with lenvatinib, toripalimab, and HAIC.[26] Overall, combining HAIC with systemic therapy for uHCC appears to be a rational approach, as it may significantly enhance treatment outcomes.

In this study, 19 patients (14.0%) achieved disease downstaging and subsequently received curative therapy, with 18 undergoing curative resection and 1 receiving curative ablation. In comparison, the ORIENT-32 trial reported that only 4% of uHCC patients treated with anti-PD-1 inhibitor and bevacizumab biosimilars achieved disease downstaging and received curative therapy.[10] One possible explanation for this discrepancy is that HAIC can deliver stable high concentrations of chemotherapeutic agents directly to the tumor site and can be administered repeatedly, leading to significant tumor shrinkage. As the tumor burden decreases, the efficacy of systemic therapy may be enhanced.[27] Notably, our conversion resection rate is comparable to recent findings from combination therapies that integrate antiangiogenic agents, anti-PD-1 inhibitor, and HAIC.[28] This observation suggests that adding HAIC to systemic therapy may increase the likelihood of conversion surgery for uHCC patients.

This study is the first to directly compare the efficacy of bevacizumab plus either an anti-PD-1 or an anti-PD-L1 inhibitor, in combination with HAIC, for initially uHCC. Efficacy analysis revealed no statistically significant differences in OS, PFS, or ORR between the BP1-HAIC and BPL-HAIC groups. Furthermore, both univariate and multivariate analyses indicated that the treatment groups were not independent risk factors for PFS or OS. The absence of such differences may be attributed to the shared mechanism of action between anti-PD-1 and anti-PD-L1 inhibitors, both of which are capable of blocking the PD-1/PD-L1 interaction and restoring the antitumor activity of T cells.[29] In HCC, PD-1 is primarily expressed on activated T cells and B cells, while its ligands, PD-L1 and PD-L2, are mainly expressed on tumor cells and antigen-presenting cells.[30] Theoretically, anti-PD-1 antibodies inhibit the binding of PD-1 on T cells and B cells to PD-L1 and PD-L2 within the tumor microenvironment. In contrast, anti-PD-L1 antibodies prevent the interaction of PD-L1 on tumor cells to PD-1 on T cells and B cells, while also impacting antigen-presenting cell function.[31] Although earlier meta-analyses suggested that anti-PD-1 therapy provides favorable survival outcomes and a comparable safety profile to anti-PD-L1 therapy,[32] recent studies have found no significant difference between these two therapies across multiple tumor types.[33–35] Further research is warranted to better elucidate potential efficacy differences between anti-PD-1 and anti-PD-L1 antibodies in tumors.

There were no treatment-related deaths, and all AEs were controllable. The treatment-related AEs of the triple combination therapy were tolerable. No unexpected or new toxic effects related to single-agent bevacizumab, anti-PD-1/anti-PD-L1 inhibitors, or HAIC have been reported.[36–38] Although triple combination therapy has been observed to cause grade 3–4 elevated AST (34.6%) and ALT (12.5%) levels, which may be explained by liver toxicity associated with HAIC, the number of patients who discontinued treatment due to AEs was low and AEs could be controlled by dose modification and symptomatic treatment. The incidence of gastrointestinal bleeding, a potentially life-threatening syndrome, was 5.1% in our study, which is consistent with the rates reported in the IMbrave150 and ORIENT-32 studies.

This study has several limitations. First, the retrospective design may introduce unintentional biases. Given that 86% of the patients had HBV-related HCC, further investigations are warranted to assess the efficacy and safety of triple combination therapy in patients with non-HBV- and non-HCV-related HCC. Second, the choice of treatment among patients in our study may have been influenced by economic conditions, medical insurance, and other factors, which, in turn, could have introduced biases and potentially impacted patient outcomes, particularly because the anti-PD-1 inhibitors in our study were more affordable than the anti-PD-L1 inhibitors. Third, to confirm our findings and enhance their generalizability, the results of this study need to be validated in a prospective multicenter randomized clinical trial.

Conclusion

In summary, the triple combination of bevacizumab, anti-PD-1/PD-L1 inhibitors, and HAIC as a first-line treatment for uHCC demonstrated significant therapeutic efficacy and a promising tumor response. No notable differences in outcomes

were observed between the BP1-HAIC and BPL-HAIC groups. The adverse effects of this combination therapy were manageable and acceptable in real-world clinical practice.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Statement of Ethics

This study does not contain patient-identifiable data. Consent from individuals involved in this study was not required. The study protocol conforms to the Declaration of Helsinki and Good Clinical Practice Guidelines. The Ethics Committee of Sun Yat-sen University Cancer Center reviewed the study protocol and waived the need for informed consent.

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Disclosure

The authors declare that they have no competing interests.

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