Original Article

Phase II trial of hepatic arterial infusion chemotherapy plus bevacizumab and toripalimab for advanced biliary tract cancers: efficacy, safety, and exploratory analysis

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Background: Chemotherapy combined with immune checkpoint inhibitor have prolonged survival of patients with advanced biliary tract cancers (BTCs), and the previous studies showed the synergistic anti-tumor effect of chemotherapy, anti-angiogenesis therapy, and immunotherapy. Hepatic arterial infusion chemotherapy (HAIC) achieved a higher tumor response and survival benefit in previous phase II studies for advanced BTCs. Thus, we conducted this phase II trial to evaluate the efficacy and safety of HAIC combined with bevacizumab and toripalimab for advanced BTCs.

Methods: Treatment-naïve participants with advanced BTCs were recruited for this phase II trial. Combination therapy, comprising HAIC with bevacizumab (300 mg, day 1), oxaliplatin (40 mg/m^2, 2 h, days 1–3), and 5-fluorouracil (800 mg/m^2, 22 h, days 1–3) plus intravenous toripalimab (240 mg, day 1 before HAIC), was repeated every 4 weeks for a maximum of six consecutive cycles. Intravenous toripalimab (240 mg) and bevacizumab (300 mg) were administered every 4 weeks as maintenance treatment. The primary endpoint was objective response rate (ORR) according to Immune-Modified Response Evaluation Criteria in Solid Tumors criteria, and the secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Olink proximity extension assay with a Target 96 Immuno-Oncology panel was exploratory investigated.

Results: Between July 2020 and January 2022, 32 participants were enrolled. The ORR was 84.38%, and the disease control rate was 96.88%. Median PFS and OS were 13.20 months [95% confidence interval (CI): 8.93–17.47] and 19.0 months (95% CI: 12.22–25.78), respectively. Grade 3 or higher adverse events (AEs) were observed in 10 participants (31.25%), and the most frequent grade 3 or higher AEs were elevated ALT/AST (4/32, 12.50%), elevated total bilirubin (3/32, 9.38%), and neutropenia (3/32, 9.38%). In exploratory analysis, Child-Pugh B [hazard ratio (HR): 22.65, 95% CI: 3.66–140.08, P=0.001] and high level of macrophage metalloproteinase-12 (HR: 5.99, 95% CI: 1.60–22.37, P=0.008) were indicated as the risk factors related to worse PFS.

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Conclusions: HAIC combined with bevacizumab and toripalimab may serve as an improved first-line treatment for advanced BTCs, which require a randomized control trial for verification.
Trial Registration: This trial is registered at ClinicalTrail.gov (NCT04217954).

Keywords: Hepatic arterial infusion chemotherapy (HAIC); advanced biliary tract cancers (advanced BTCs); bevacizumab; toripalimab

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Introduction

Biliary tract cancers (BTCs), which arise from the biliary epithelial cells, are classified into gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (1,2). Most patients with BTCs are diagnosed at advanced stages and are, therefore, not candidates for surgery (2,3).

Gemcitabine plus cisplatin (GemCis) remains the mainstay first-line systemic treatment for advanced BTCs, with a median overall survival (OS) of 11.7 months, as reported in the ABC-02 trial (4). Recently, the combination of durvalumab or pembrolizumab and GemCis regimen was demonstrated to prolong the survival of patients with advanced BTCs in the TOPAZ-1 and KEYNOTE-966 studies; however, the improvements in survival were limited, with median OS of 12.9 and 12.7 months, respectively (5,6).

Hepatic arterial infusion chemotherapy (HAIC), which delivers chemotherapeutic agents directly to liver tumors to achieve high local drug concentrations, may be safer and more effective for patients with hepatobiliary malignancies (7). High tumor control and significant survival benefits of HAIC have been reported in recently published phase II trials for BTCs (8-11). Toripalimab is a humanized programmed cell death protein-1 (PD-1) monoclonal antibody that could prevent the binding of PD-1 with programmed cell death ligand-1 (PD-L1) and 2 (PD-L2) (12). In recent years, toripalimab plus chemotherapy showed synergistic effect and encouraging efficacy for various cancers, such as esophageal carcinoma, lung cancer, and nasopharyngeal carcinoma (13-15).

Vascular endothelial growth factor (VEGF) is a crucial regulator of angiogenesis in BTCs and a critical molecule that regulates immunosuppression by inhibiting dendritic cell differentiation and activity (16,17). VEGF inhibitors facilitate vascular modification and T-cell infiltration of tumors, achieving a synergic effect when combined with PD-1/PD-L1 inhibitors and enhancing the efficacy of chemotherapy (18-20). Recently, the results of the IMbrave 151 trial, which compared the efficacies of atezolizumab, bevacizumab plus cisplatin and gemcitabine to atezolizumab

Highlight box

Key findings
- The objective response rate was 84.38% per Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST) criteria and 75% per RECIST 1.1 criteria, with the disease control rate of 96.88%.
- The median progression-free survival (PFS) and overall survival were 13.20 and 19.0 months, respectively.
- Ten out of 32 participants experienced grade 3 or higher treatment-related adverse events.
- High level of macrophage metalloproteinase-12 was a potential biomarker related to worse PFS.

What is known and what is new?
- Recently, hepatic arterial infusion chemotherapy (HAIC) has been reported with high tumor control and significant survival benefits for advanced biliary tract cancers (BTCs). Vascular endothelial growth factor (VEGF) is a crucial regulator of angiogenesis in BTCs and a critical molecule that regulates immunosuppression by inhibiting dendritic cell differentiation and activity, and VEGF inhibitors facilitate vascular modification and T-cell infiltration of tumors, achieving a synergic effect when combined with programmed cell death-1 (PD-1)/programmed cell death-ligand 1 inhibitors and enhancing the efficacy of chemotherapy.
- This is the first phase II trial to investigate the efficacy of HAIC combined with PD-1 inhibitor and bevacizumab for advanced BTCs, and the combination therapy presented with great efficacy and acceptable safety profile.

What is the implication, and what should change now?
- HAIC combined with bevacizumab and toripalimab may represent an effective first-line treatment for advanced BTCs, and MMP12 may serve as a predictor of worse prognosis for this triple combination treatment.

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plus cisplatin and gemcitabine as first-line treatment for patients with advanced BTCs, with a median progression-free survival (PFS) of 8.4 *vs.* 7.9 months [hazard ratio (HR): 0.76], indicated a synergistic therapeutic effect of this triple combination treatment (21).

Therefore, we conducted the present open-label, single-arm, single-center, phase II trial to evaluate the efficacy and safety of a triple combination therapy comprising HAIC, bevacizumab (a VEGF inhibitor), and toripalimab (a PD-1 inhibitor) as first-line treatment for advanced BTCs. We present this article in accordance with the CONSORT reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-463/rc).

Methods

Study design, ethics statement, and participants

This open-label, single-arm, single-center, phase II trial was approved by the Ethics Committee of the Peking University Cancer Hospital (No. 2020YJZ38) and registered at Clinicaltrials.gov (NCT04217954). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice (as revised in 2013). Written informed consent was obtained from all the patients.

Key eligibility criteria were as follows: (I) histopathological/cytological diagnosed advanced unresectable BTCs including iCCA, pCCA, and GBC, and confirmed by multidisciplinary team; (II) no previous loco-regional or systemic therapies; (III) ages of 18–80 years; (IV) at least one measurable lesion; (V) Eastern Cooperative Oncology Group (ECOG) performance status <2; (VI) Child-Pugh A or B (≤7); and (VII) adequate organ function, including hemoglobin level ≥90 g/L, absolute neutrophil counts $\geq 1.5\times10^9$/L, platelet counts $\geq 100\times10^9$/L, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤2.5-fold the upper limit of normal (ULN), serum total bilirubin (TBiL) levels ≤5-fold ULN, serum creatinine levels ≤1.5-fold ULN, and serum albumin level ≥30 g/L. Participants who did not meet the inclusion criteria or refused to participate in the trial were excluded. The detailed inclusion and exclusion criteria are listed at Clinicaltrials.gov (NCT04217954).

Procedures and treatment

HAIC was administered through a percutaneously implanted port-catheter system using the fix-catheter-tip method as previously described (22-25). The combination therapy, which was repeated every 4 weeks, consisted of HAIC and intravenous toripalimab (240 mg, day 1 prior to HAIC), with the HAIC regimen of bevacizumab (300 mg, day 1), oxaliplatin (40 mg/m^2, 2 h, days 1–3), and 5-fluorouracil (800 mg/m^2, 22 h, days 1–3). A maximum of 6 consecutive HAIC cycles were administered, followed by intravenous infusion of toripalimab (240 mg) and bevacizumab (300 mg) every 4 weeks as maintenance treatment until tumor progression, participant death, or participant withdrawal, whichever occurred first. The doses of bevacizumab, toripalimab, and intra-arterial chemotherapeutic agents were adjusted or discontinued according to treatment-related adverse events (AEs), and the subsequent treatment after the tumor progression was chosen based on the clinicians' and participants' decision.

Follow-up and assessments

Physical examinations, ECOG performance status assessment, routine blood tests, liver and kidney function assessments, serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, abdominal contrast-enhanced CT/MRI, and chest radiography/CT were performed after every two cycles of treatment for evaluation until disease progression. The survival follow-up procedure was continued every 3 months after discontinuation or completion of the trial.

Two radiologists (who were blinded to the treatment protocol) with more than 10 years of experience in abdominal imaging diagnosis, assessed the follow-up CT/MRI images to reach a consensus. Tumor response was evaluated according to the Immune-Modified Response Evaluation Criteria in Solid Tumors (imRECIST) criteria (26), and post hoc evaluation was performed according to RECIST 1.1 criteria (27).

Endpoints

The primary endpoint was objective response rate (ORR) per imRECIST criteria, and the secondary endpoints were PFS, OS, and safety. PFS was defined as the date from the initiation of HAIC to disease progression or participant death, whichever occurred first. OS was calculated from the initiation of HAIC to death or last follow-up. The duration of response (DoR) was defined as the interval between the date of the first documented complete response (CR)

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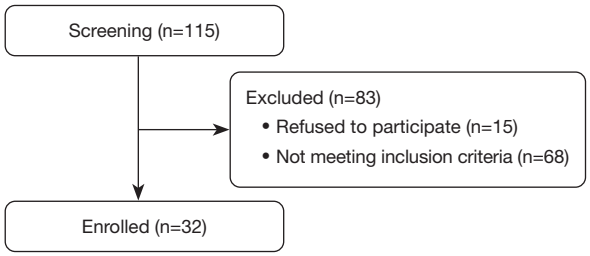

Figure 1 Participant flowchart.

or partial response (PR), to the date of first documented confirmed progressed disease (PD) or death. Treatment-related AEs were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Exploratory endpoint was peripheral blood protein levels before the initiation of the study treatment.

Exploratory analysis

Olink proximity extension assay with a Target 96 Immuno-Oncology panel was employed to determine the plasma levels of 92 proteins as biomarkers. The assay protocol was available online (http://olink.com/content/uploads/2022/05/olink-target-96-short-instructions.pdf). The obtained results were presented as normalized protein expression (NPX) values, which were on log2 scale and obtained by normalizing Ct-values against extension control, interpolate control and a correction factor. The high NPX value corresponds to a high protein concentration and can be linearized by using the formula 2^{NPX}. Values below the lowest level of detection for each marker, based on the negative controls analyzed in each run, were set to limit of detection (LOD) value.

Statistical analysis

A Simon's two-stage design was adopted in this study, with ORR as the primary endpoint. The ORR was 26.1% in the ABC-02 trial; therefore, we assumed an ORR of 50% in this trial. The planned sample size was 29 based on α=0.05, power =0.8, and CR or PR achievement in 11 participants. If no more than 3 of the initial 11 participants were evaluated as achieving CR or PR, the trial was to be terminated. Considering an estimated dropout rate of 10%, an enrollment of 32 participants was required.

Continuous and categorical variables were presented as mean ± standard deviation and frequencies, respectively. The chi-square test was used to compare categorical variables, and the Kruskal-Wallis *H* test was used for the comparison of continuous variables. OS and PFS were assessed using Kaplan-Meier method, and compared using log-rank test. Student's *t*-test was employed for the Olink standard differential analysis to calculate the expression differences of proteins in standardized NPX data under different experimental conditions. The Cox proportional hazards model was used in univariate and multivariable survival analysis, and variates with P<0.05 in univariate analysis were analyzed in multivariable analysis. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS v.23.0 software (IBM Corp, Armonk, NY, USA) or R software (R version 4.2.0, http://www.r-project.org).

Results

Participants characteristics

From July 2020 to January 2022, 32 treatment-naïve participants (20 men and 12 women) with advanced BTCs were enrolled in this trial, including 11 with iCCA, 17 with pCCA, and 4 with GBC (*Figure 1*). The age was 62.06±8.82 years (range, 41.0–76.0 years). Extrahepatic metastasis disease, which included lymph node and distant organ metastasis, was detected in 18 (56.25%) participants, including 12 (37.50%) with only lymph node metastasis and 6 (18.75%) with distant organ metastasis. Twenty participants underwent biliary drainage before the study treatment for obstructive jaundice, and the study treatment was initiated until the total bilirubin level decreased to less than five times the ULN after biliary drainage.

A total of 168 cycles of study treatment were performed in this trial (5.25±1.22 cycles; range, 2–6 cycles), and 21 (65.63%) participants received maintenance treatment (5.95±5.41 cycles; range, 1–20 cycles). Seventeen (53.13%) participants received subsequent treatments such as HAIC with another regimen, surgery, and systemic chemotherapy after the tumor progression. Two participants underwent surgical resection after the study treatment, and one achieved pathological CR (*Figure 2*). Participants characteristics are listed in *Table 1*.

The survival follow-up procedures were continued until July 18, 2024, with the median follow-up time of 37.20 months. Until the last follow-up, tumor progression was confirmed in 20 (62.50%) participants, and 22 (68.75%) participants died. As second-line treatment, one participant

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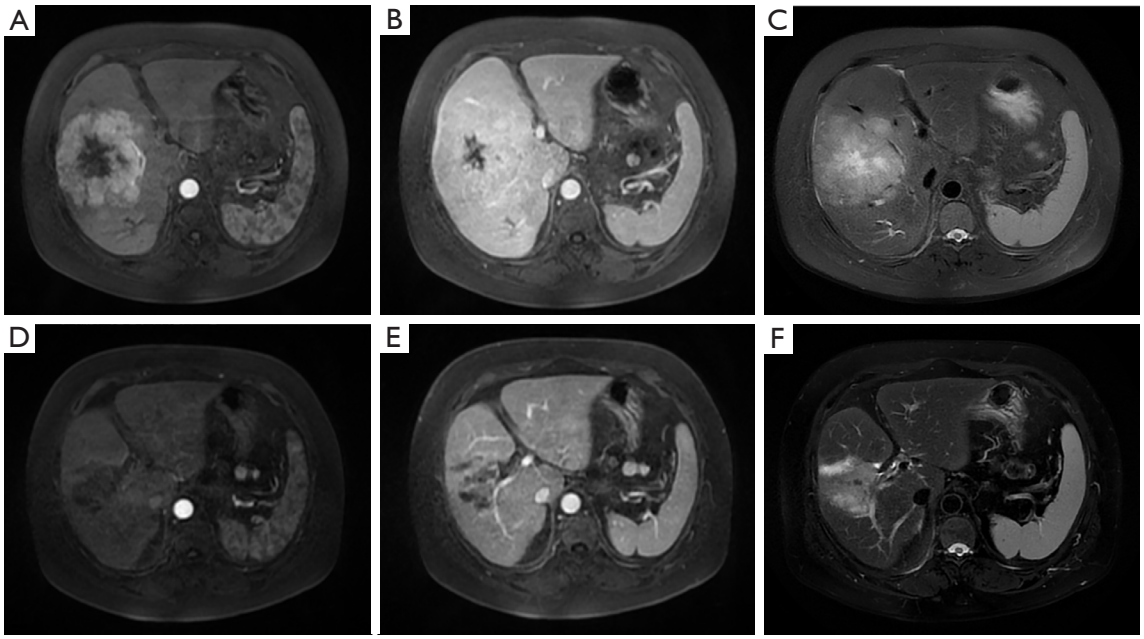

Figure 2 MRI images of a representative participant. A participant in 40s was diagnosed with intrahepatic cholangiocarcinoma after liver puncture biopsy. (A-C) A giant tumor in the right lobe of the liver was detected on the contrast-enhanced MRI of the arterial and venous phases before treatment. The CEA level was 1.53 ng/mL, and that of CA19-9 was 2,050 U/mL. (D-F) After six cycles of treatment, the tumor had shrunk further in size and enhanced portion, and the CA19-9 (38.04 U/mL) decreased. Tumor response was designated as partial response according to the imRECIST criteria. The participant received intravenous bevacizumab and toripalimab as maintenance treatment, and the CA19-9 level decreased further to normal. Subsequently, surgical resection was performed, and pathological examination did not detect residual tumor cells in the lesion or surrounding liver tissue (pCR). The participant was alive without tumor recurrence on July 18, 2024 (OS, 33.40 months). MRI, magnetic resonance imaging; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; imRECIST, Immune-Modified Response Evaluation Criteria in Solid Tumors; pCR, pathological complete response; OS, overall survival.

received HAIC using other regimens; four received HAIC using other regimens plus immunotherapy; two received HAIC using other regimens plus oral tyrosine kinase inhibitors (TKIs), such as regorafenib and lenvatinib, and immunotherapy; three received oral TKIs plus immunotherapy; three received systemic chemotherapy; one received systemic chemotherapy plus immunotherapy; and two received oral TKI.

Tumor response

Confirmed CR or PR was achieved in six of the first 11 enrolled participant, and the trial was therefore continued for full enrollment. With the proceeding of study treatment, two of the five participants who previously achieved stable disease (SD) achieved CR or PR among the first 11 enrolled participants. Finally, CR, PR, SD, and PD per imRECIST criteria were achieved in 3 (9.38%), 24 (75.0%), 4 (12.50%), and 1 (3.13%) participant, respectively, in all enrolled participants (*Figure 3*). The confirmed ORR was 84.38%, with the confirmed ORRs amongst participants with iCCA, pCCA, and GBC of 72.7%, 88.2%, and 100%, respectively. The disease control rate (DCR) per imRECIST criteria was 96.88%. The post hoc evaluation according to RECIST 1.1 criteria showed that the confirmed ORR was 75% (24/32), with 1 CR (3.13%), 23 PR (71.88%), 7 SD (21.88%), and 1 PD (3.13%) (*Figure 2*, *Table 2*).

Survival

The median OS and PFS were 19.0 months [95% confidence interval (CI): 12.22–25.78] and 13.20 months (95% CI: 8.93–17.47) (*Figure 4*), respectively, with the median DoR of 11.40 months (95% CI: 8.04–14.76). The post hoc evaluation showed that the median local PFS, which was identified as the period between the initiation of

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Table 1 Participants characteristics

Characteristics	N (%)
Subtypes	
iCCA	11 (34.38)
pCCA	17 (53.13)
GBC	4 (12.50)
Age (years)	
<60	12 (37.50)
≥60	20 (62.50)
Gender	
Male	20 (62.50)
Female	12 (37.50)
Hepatitis	
No	27 (84.38)
Hepatitis B	4 (12.50)
Hepatitis C	1 (3.13)
Child-Pugh class	
A	23 (71.88)
B	9 (28.13)
Degree of differentiation	
Moderately differentiated	9 (28.13)
Poorly differentiated	6 (18.75)
Unknown	17 (53.13)
Disease status	
Liver confined disease	14 (43.75)
Extrahepatic metastatic disease	18 (56.25)
CEA (ng/mL)	
<10	24 (75.0)
≥10	8 (25.0)
CA19-9 (U/mL)	
<200	12 (37.50)
≥200	20 (62.50)
ECOG performance status	
0	19 (59.38)
1	13 (40.63)
Jaundice	
No	11 (34.38)
Yes	21 (65.63)

iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; GBC, gallbladder cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group.

the study treatment and disease progression of the primary tumor site, or death from any cause, was 13.90 months (95% CI: 9.70–18.10).

The median OS and PFS were similar among participants with iCCA, pCCA, and GBC, with the median OS of 19.0 *vs.* 21.60 *vs.* 12.60 months (P=0.26) and the median PFS of 14.40 *vs.* 14.40 *vs.* 8.80 months (P=0.36), respectively. Both median OS and PFS in participants with liver confined disease were numerically longer than those in participants with extrahepatic metastatic disease (25.70 *vs.* 14.60 months and 16.40 *vs.* 9.60 months, respectively), while neither the differences were statistically significant (P=0.53 and P=0.51, respectively).

Safety

All treatment-related AEs were manageable in this trial, and most participants recovered to normal before the next cycle of treatment (*Table 3*). Catheter dislocation was detected in one participant three months after the implantation of a port-catheter system; therefore, delivery of HAIC with a temporary indwelling catheter in the proper hepatic artery was adopted.

Thirty-one participants (96.88%) experienced treatment-related AEs of any grade, whereas grade 3 or higher treatment-related AEs were observed in only 10 participants (31.25%). The most frequent grade 3 or higher treatment-related AEs were elevated ALT/AST (4/32, 12.50%), elevated total bilirubin (3/32, 9.38%), and neutropenia (3/32, 9.38%). The study did not report any cases of symptomatic cholangitis during or after HAIC. One participant died because of a gallbladder-colon fistula and liver abscess after treatment.

Immunotherapy-related AEs were observed in three participants, including 1 hypothyroidism (3.13%), 1 diabetes (3.13%), and 1 grade 3 elevated creatine kinase (3.13%). The participant with the elevated creatine kinase recovered to normal without any medical intervention, while the participant who experienced hypothyroidism was administered levothyroxine, and the other participant was injected with insulin to treat diabetes.

Treatment delay or dose reduction of HAIC due to the grade 3 or higher AEs was observed in 6 participants (18.75%). Toripalimab interruption was required for 1 participant (3.13%), which was caused by elevated creatine kinase, and was resumed after the creatine kinase level reverted to normal. HAIC and toripalimab therapy were not discontinued in any participant.

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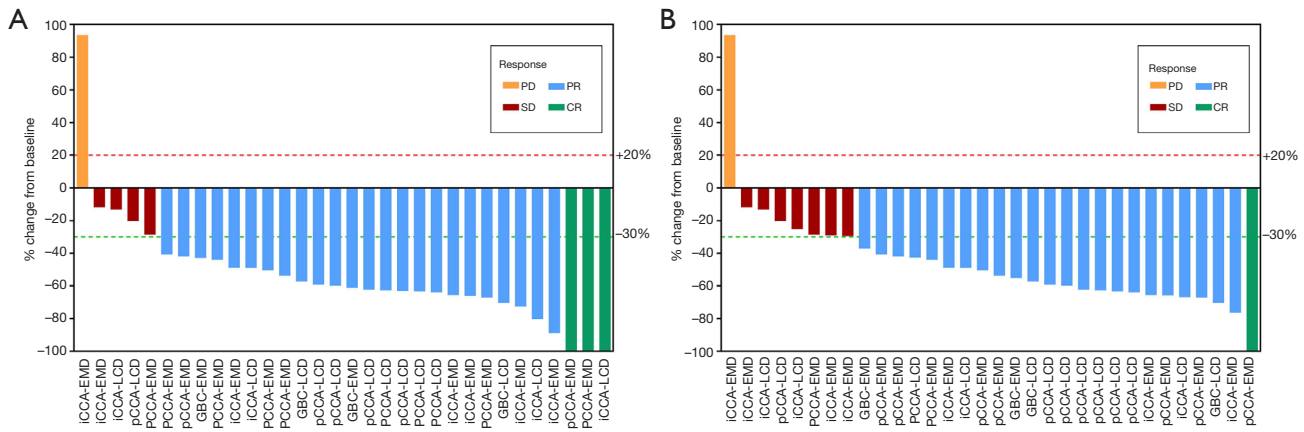

Figure 3 Waterfall plot of tumor responses. (A) Tumor response per imRECIST criteria. (B) Tumor response per RECIST 1.1 criteria. iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; GBC, gallbladder cancer; LCD, liver confined disease; EMD, extrahepatic metastatic disease; CR, complete response; PR, partial response; SD, stable disease; PD, progressed disease; imRECIST, Immune-Modified Response Evaluation Criteria in Solid Tumors.

Table 2 Tumor response

Response	imRECIST (n=32)	RECIST 1.1 (n=32)
CR, n (%)	3 (9.38)	1 (3.13)
PR, n (%)	24 (75.00)	23 (71.88)
SD, n (%)	4 (12.50)	7 (21.88)
PD, n (%)	1 (3.13)	1 (3.13)
Confirmed ORR (%)	84.38	75
DCR (%)	96.88	96.88

imRECIST, Immune-Modified Response Evaluation Criteria in Solid Tumors guideline; RECIST 1.1, Response Evaluation Criteria in Solid Tumors guideline (version 1.1); CR, complete response; PR, partial response; SD, stable disease; PD, progressed disease; ORR, objective response rate; DCR, disease control rate.

Exploratory analysis

Blood samples were obtained from 29 participants before the initiation of the study treatment. All of the samples passed the quality control, and were used for plasma biomarkers analysis of 92 proteins.

The participants were divided into responder group (CR or PR in tumor response) and non-responder group (SD or PD in tumor response), with 24 in responder group and 5 in non-responder group. The NPX value of 13 proteins in the non-responder group were significantly higher than those in the responder group, including mucin-16 (MUC-16), tumor necrosis factor ligand superfamily member 6 (FASLG), hepatocyte growth factor (HGF), cytotoxic and regulatory T-cell molecule (CRTAM), monocyte chemotactic protein-2 (MCP-2), T-cell surface glycoprotein CD8 alpha chain (CD8A), decorin (DCN), macrophage colony-stimulating factor 1 (CSF-1), tumor necrosis factor ligand superfamily member 12 (TWEAK), C-C motif chemokine 3 (CCL3), natural cytotoxicity triggering receptor (NCR1), tumor necrosis factor receptor superfamily member 12A (TNFRSF12A), and C-C motif chemokine 4 (CCL4) (*Figure 5*).

The median NPX value was adopted as the cut-off value for each protein to differentiate high and low protein levels. Low protein levels of CSF-1, T-cell surface glycoprotein CD5 (CD5), angiopoietin-2 (ANGPT2), interferon gamma (IFN-gamma), and macrophage metalloproteinase-12 (MMP12) before the study treatment were associated with better PFS (*Figure 6*). After the univariate and multivariable COX analysis, Child-Pugh B (HR: 22.65, 95% CI: 3.66–140.08, P=0.001) and high level of MMP12 (HR: 5.99, 95% CI: 1.60–22.37, P=0.008) were indicated as the independent risk factors related to worse PFS (*Table 4*).

Discussion

This phase II trial demonstrated the encouraging efficacy and safety of triple combination therapy with HAIC, bevacizumab and toripalimab as a first-line treatment for advanced BTCs, as indicated by ORR, DCR, median OS, and median PFS of 84.38%, 96.88%, 19.0 months, and

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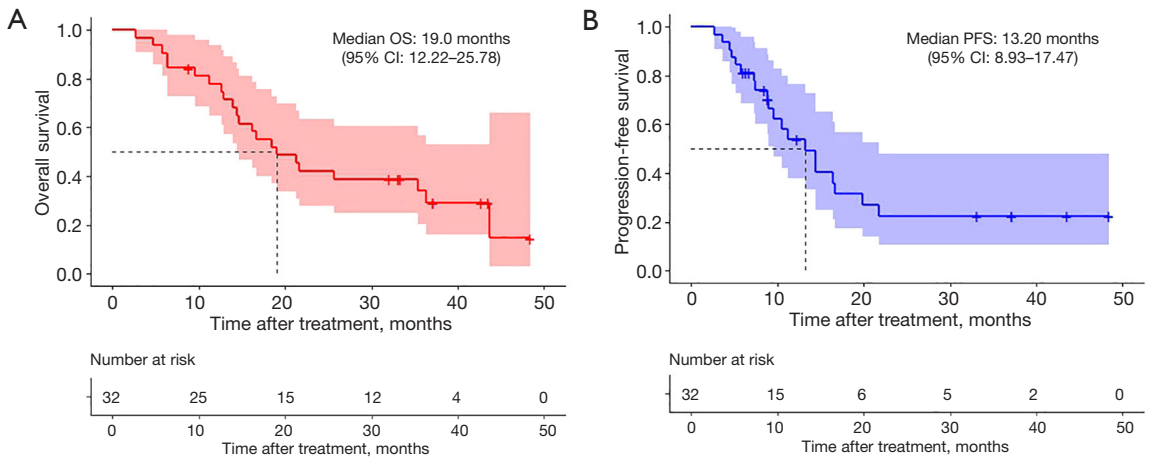

Figure 4 Survival curves. (A) OS; (B) PFS. OS, overall survival; PFS, progression-free survival.

Table 3 Adverse events

Events	Any grade, n (%)	Grade 3 or higher, n (%)
Any adverse event	31 (96.88)	10 (31.25)
Adverse event leading to HAIC delay or reduction	7 (21.88)	6 (18.75)
Adverse event leading to toripalimab interruption or reduction	1 (3.13)	1 (3.13)
Adverse events leading to HAIC or toripalimab discontinuation	0	0
Adverse event leading to death	1 (3.13)	1 (3.13)
Gastrointestinal events		
Nausea	21 (65.63)	0
Vomiting	13 (40.63)	0
Diarrhea	1 (3.13)	1 (3.13)
Stomach ache	16 (50.0)	0
Hepatotoxicity		
Elevated ALT/AST	17 (53.13)	4 (12.50)
Hyperbilirubinemia	12 (37.50)	3 (9.38)
Hematotoxicity		
Leukopenia	13 (40.6)	1 (3.13)
Thrombocytopenia	16 (50.0)	2 (6.25)
Neutropenia	8 (25.0)	3 (9.38)
Anemia	13 (40.63)	0
Neurological toxicity	10 (31.25)	0
Fever	18 (56.25)	0

HAIC, hepatic arterial infusion chemotherapy; ALT, alanine transaminase; AST, aspartate transaminase.

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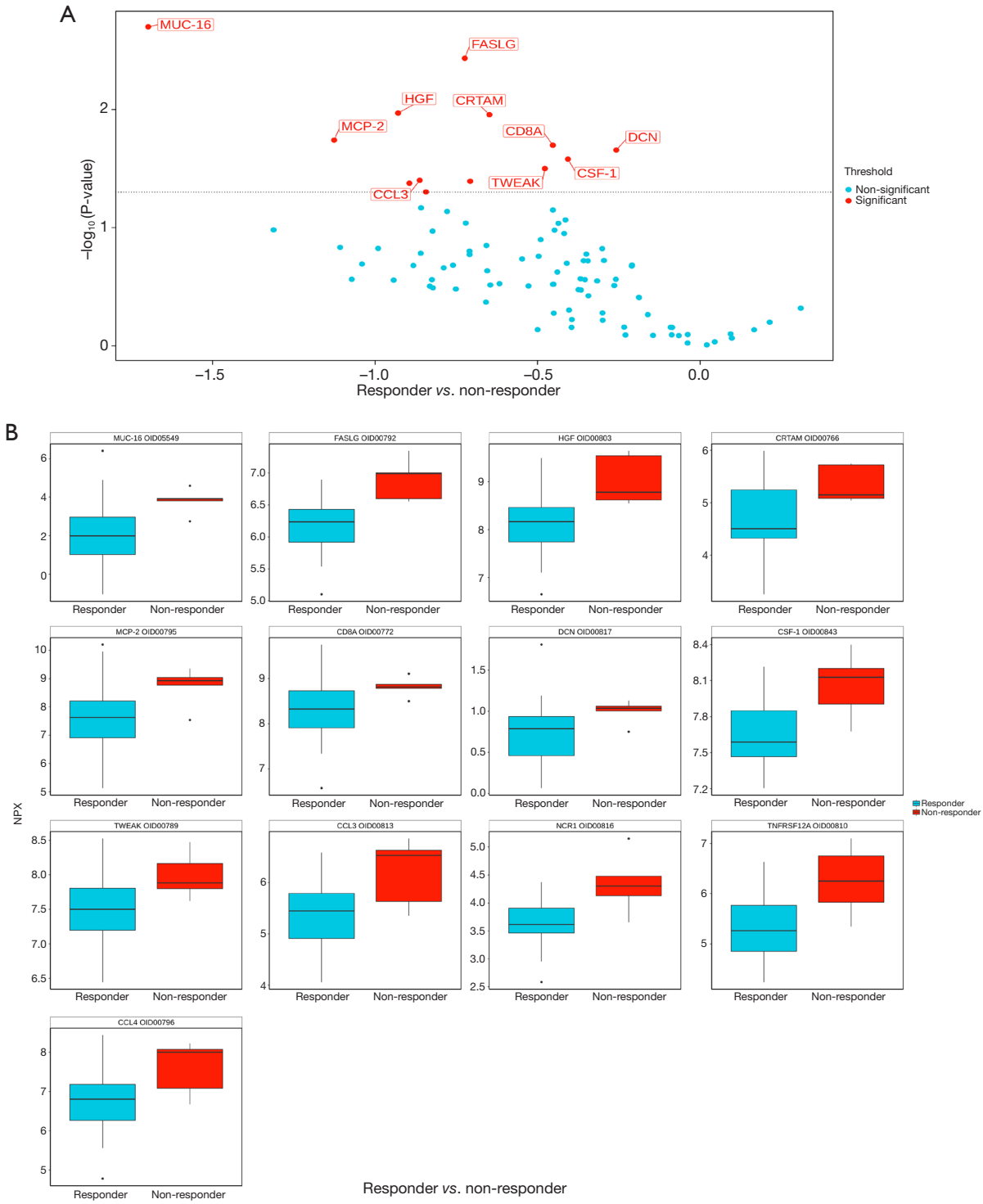

Figure 5 Proteins with significant difference between responder group and non-responder group. (A) Volcano plot. (B) Box plot. NPX, normalized protein expression.

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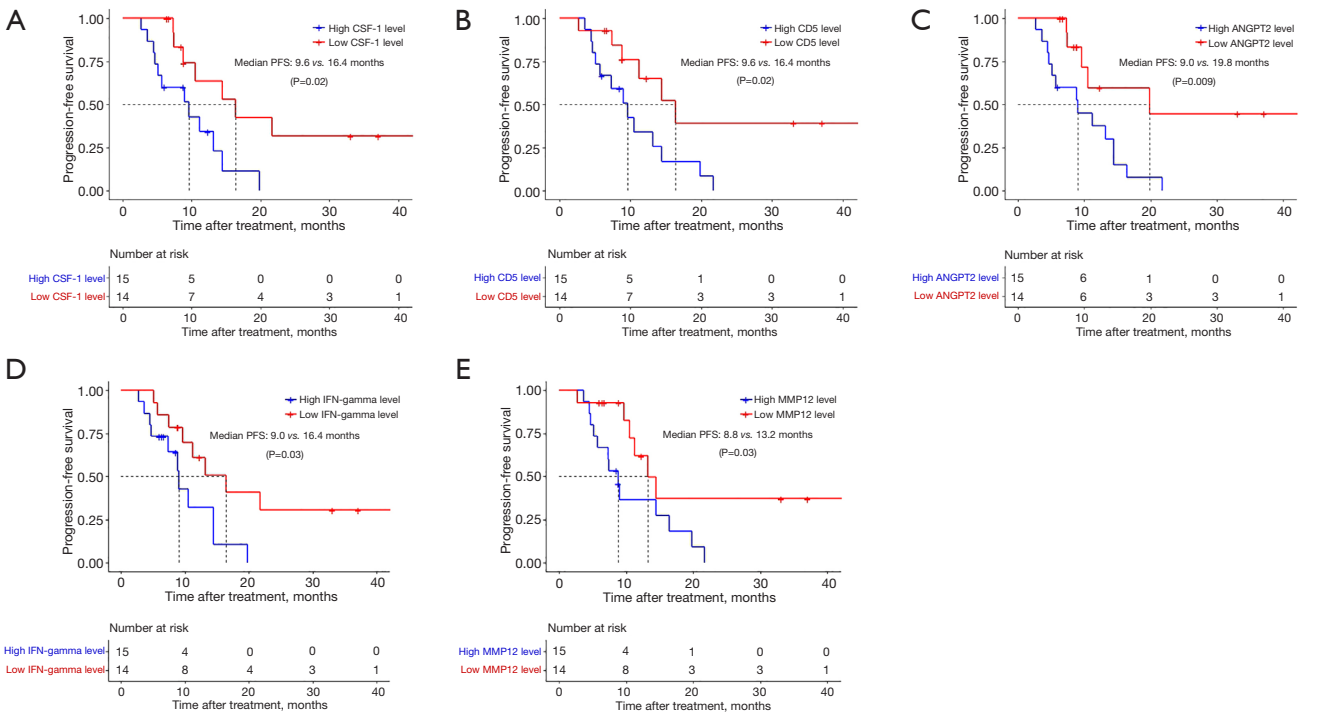

Figure 6 High level of different proteins related to worse PFS of participants. (A) CSF-1. The median PFS was 9.6 *vs.* 16.4 months (P=0.02). (B) CD5. The median PFS was 9.6 *vs.* 16.4 months (P=0.02). (C) ANGPT2. The median PFS was 9.0 *vs.* 19.8 months (P=0.009). (D) IFN-gamma. The median PFS was 9.0 *vs.* 16.4 months (P=0.03). (E) MMP12. The median PFS was 8.8 *vs.* 13.2 months (P=0.03). PFS, progression-free survival; CSF-1, macrophage colony-stimulating factor 1; CD5, T-cell surface glycoprotein CD5; ANGPT2, angiopoietin-2; IFN-gamma, interferon gamma; MMP12, macrophage metalloproteinase-12.

13.20 months, respectively. Notably, the median OS of the participants with liver confined disease was 25.70 months. Regarding the safety profile, grade 3 or higher treatment-related AEs were observed in only 10 participants (31.25%), and all AEs were manageable.

There is growing interest in the triple synergistic effect of combining chemotherapy, immunotherapy, and anti-VEFG therapy in cancer treatment. Bevacizumab (a VEGF inhibitors) could facilitate the infiltration of tumors by T-cells and improve the antigen-presenting capacity of circulating dendritic cells, suggesting the stimulation and activation of the immune system when combined with immune checkpoint inhibitors (18,28-31). Meanwhile, bevacizumab is beneficial for the normalization of tumor vessels, facilitating drug delivery, and enhancing the efficacy of chemotherapy (19,20). Chemotherapeutic agents, such as gemcitabine, cisplatin, oxaliplatin, and 5-fluorouracil, could modulate the immune system through direct immunostimulatory mechanisms, downregulation of the immunosuppressive microenvironment, and increased immunogenicity (32,33). The combination of chemotherapy combined with PD-1/PD-L1 inhibitors have been demonstrated to be more effective in lung, esophageal, and gastric cancers, and confirmed by the TOPAZ-1 and KEYNOTE-966 trials in patients with advanced BTCs (5,6,34,35).

The IMbrave151 trial was the first randomized study to evaluate the combination of PD-L1 inhibitor, VEGF inhibitors, and systemic chemotherapy for advanced BTCs. The trial demonstrated an extended median PFS after treatment with bevacizumab combined with atezolizumab plus gemcitabine and cisplatin (8.4 *vs.* 7.9 months, HR: 0.76), although the statistical significance was not met (21). Another phase II trial evaluated the triple combination of toripalimab (PD-1 inhibitor), lenvatinib, and chemotherapy with the GEMOX regimen for advanced iCCA (36). The trial yielded some promising results, with an ORR, median OS, and median PFS of 80%, 22.5 months, and

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Table 4 Univariate and multivariable analyses of factors related to progression-free survival

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Subtypes				
iCCA	1			
pCCA	0.43 (0.16–1.15)	0.09		
GBC	1.46 (0.28–7.62)	0.66		
Age (years)				
<60	1			
≥60	1.05 (0.41–2.67)	0.93		
Gender				
Male	1			
Female	0.90 (0.35–2.27)	0.82		
Hepatitis				
No	1			
Hepatitis B	1.03 (0.23–4.62)	0.97		
Hepatitis C	0 (0.000–)	0.99		
Child-Pugh class				
A	1		1	
B	5.06 (1.72–14.92)	0.003	22.65 (3.66–140.08)	0.001
Degree of differentiation				
Moderately differentiated	1			
Poorly differentiated	0.67 (0.16–2.75)	0.57		
Disease status				
Liver confined disease	1			
Extrahepatic metastatic disease	1.32 (0.52–3.37)	0.57		
CEA level				
<10 ng/mL	1		1	
≥10 ng/mL	3.76 (1.38–10.22)	0.009	2.75 (0.84–8.98)	0.10
CA19-9 level				
<200 U/mL	1			
≥200 U/mL	1.45 (0.56–3.72)	0.44		
ECOG performance status				
0	1			
1	2.26 (0.90–5.64)	0.08		

Table 4 (*continued*)

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Table 4 (*continued*)

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Jaundice				
No	1			
Yes	1.09 (0.39–3.09)	0.87		
CSF-1 level				
Low	1		1	
High	3.24 (1.18–8.90)	0.02	3.48 (0.76–16.04)	0.11
CD5 level				
Low	1		1	
High	2.91 (1.10–7.74)	0.03	0.19 (0.03–1.09)	0.06
ANGPT2 level				
Low	1		1	
High	3.67 (1.30–10.40)	0.01	2.83 (0.83–9.64)	0.10
IFN-gamma level				
Low	1		1	
High	2.77 (1.05–7.30)	0.04	3.48 (0.96–12.63)	0.058
MMP12 level				
Low	1		1	
High	2.84 (1.07–7.58)	0.04	5.99 (1.60–22.37)	0.008

HR, hazard ratio; CI, confidence interval; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; GBC, gallbladder cancer; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; CSF-1, macrophage colony-stimulating factor 1; CD5, T-cell surface glycoprotein CD5; ANGPT2, angiopoietin-2; IFN-gamma, interferon gamma; MMP12, macrophage metalloproteinase-12.

10.2 months, respectively. However, 56.7% of the participants experienced grade 3 or higher AEs.

HAIC can increase the concentration of chemotherapeutic agents in liver tumors, leading to better tumor control in the liver (7). Recently, HAIC with oxaliplatin and 5-fluorouracial had shown the survival benefits for patients with advanced BTCs (9,11,37,38). Furthermore, oxaliplatin and 5-fluorouracil may kill immunogenic cells and activate the adaptive immune system and immune checkpoint inhibitors (39,40). The phenomenon that most participants with extrahepatic metastatic disease did not show progression of the extrahepatic metastatic lesions at the first and second evaluations in this trial also suggests that HAIC may enhance the systemic anti-tumor effect of immunotherapy.

To our knowledge, this is the first phase II trial to investigate the efficacy of HAIC in combination with PD-1 inhibitor and bevacizumab for advanced BTCs. The triple combination therapy showed superior outcomes compared to the recommended first-line treatment for advanced BTCs in prior published phase III trials, with a higher ORR [84.38% *vs.* 26.1% (GemCis) *vs.* 26.7% (durvalumab plus GemCis) *vs.* 29% (pembrolizumab plus GemCis)], longer PFS [13.20 *vs.* 8.0 (GemCis) *vs.* 7.2 (durvalumab plus GemCis) *vs.* 6.5 months (pembrolizumab plus GemCis)], and longer OS [19.0 *vs.* 11.7 (GemCis) *vs.* 12.9 (durvalumab plus GemCis) *vs.* 12.7 months (pembrolizumab plus GemCis)] (4-6,41). The median OS of 25.70 months achieved in the participants with liver confined disease in this trial was also encouraging. Additionally, the median PFS and OS in participants with extrahepatic metastatic disease were 9.60 and 14.60 months, respectively, and most of them got progression in both intrahepatic and

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extrahepatic lesions, which may be attributed to the higher aggressive nature of such tumors compared to those without extrahepatic metastasis.

Here, we showed that all AEs were manageable in this trial, and only 31.25% of the participants experienced grade 3 or higher AEs [31.25% *vs.* 70.7% (4) *vs.* 62.7% (5) *vs.* 70% (6) *vs.* 73% (21) *vs.* 56.7% (36)]. This may be explained as follows: the dosages of chemotherapeutic agents used for HAIC were lower than those used for systemic chemotherapy. Additionally, a 3-day circulatory infusion of HAIC reduced the toxicities of the chemotherapy. However, a gallbladder-colon fistula occurred in one participant 2 months after the initiation of the study treatment. This may be due to the quick and deep regression of the tumor in the context of tumor invasion of the colon, so that the normal tissue did not have sufficient time to heal the defect caused by the tumor disappearance. Drainage of the biliary tract, liver, and abdominal abscesses combined with antibiotic therapy and intravenous nutrition was administered when the fistula and abscessed were detected. However, the participant died 5.7 months after the initiation of treatment. Thus, this triple combination treatment should be carefully considered in patients whose tumors have severely invaded the gastrointestinal tract and other organs.

Olink proteome technology is a circulating protein biomarker test that can predict prognosis and monitor the efficacy of treatment, and can be performed using the plasma of patients without the requirement of tumor tissue (42,43). Therefore, the Olink proteome technology was employed to detect protein biomarkers in this trial owing to both its accessibility and its cost-effectiveness. In this study, participants in non-responder group presented significant higher level of MUC-16, FASLG, HGF, CRTAM, MCP-2, CD8A, DCN, CSF-1, TWEAK, CCL3, NCR1, TNFRSF12A, and CCL4 than participants in responder group. Interestingly, seven of them were identified as the biomarkers associated with tumor proliferation, invasion, and metastasis by previously published studies, including MUC-16, HGF, MCP-2, TWEAK, CCL3, TNFRSF12A, and CCL4 (44-49). Meanwhile, high level of MUC-16, FASLG, and CSF-1 have been demonstrated to be conducive to inhibit anticancer immune responses and lead immune escape (44,50,51). Therefore, we speculated the worse tumor response to the study treatment might due to the high expression of the proteins mentioned above. Additionally, high level of MMP12 was identified as one of the independent risk factors related to the worse PFS in this study. The result was consistent with the previous study which indicated MMP12 helps cancer cells grow and the elevated MMP12 expression serves as a biomarker of poor prognosis in various cancers (52). However, the results should be interpreted with caution due to the post-hoc analysis nature, limited number of participants with available and qualified blood samples for analysis, and the great quantitative differences between responder group and non-responder group. Therefore, further studies with large sample size are required to verify the results in the present study and explore the underlying mechanism related to the biomarkers mentioned above.

This trial has other limitations. First, more than 50% of participants with extrahepatic metastatic disease were enrolled, which may have reduced the maximization of survival benefits because of the progression of extrahepatic disease. Second, subsequent treatments, which depended on the decision of clinicians or participants after disease progression or treatment discontinuation may eventually affect survival results. Third, only four participants with GBC were enrolled, which may limit the generalization of the results to patients with GBC. Fourth, the status of microsatellite instability was not considered in the inclusion and exclusion criteria and was unknown to most participants, limiting subgroup comparison between participants with different extents of microsatellite instability. Fifth, the sample size was small in this phase II trial, and the results require further validation in a randomized phase III trial.

Conclusions

This phase II trial demonstrated that HAIC combined with bevacizumab and toripalimab may represent an effective first-line treatment for advanced BTCs, as supported by long survival, great tumor control, and an acceptable safety profile. Meanwhile, MMP12 may serve as a predictor of worse prognosis for this triple combination treatment. However, randomized phase III trial is required to verify these results.

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None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-463/rc

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Trial Protocol: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-463/tp

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-24-463/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Peking University Cancer Hospital (No. 2020YJZ38) and informed consent was obtained from all individual participants.

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References

1. Bridgewater JA, Goodman KA, Kalyan A, et al. Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling. Am Soc Clin Oncol Educ Book 2016;35:e194-203.
2. Khan AS, Dageforde LA. Cholangiocarcinoma. Surg Clin North Am 2019;99:315-35.
3. Chan E, Berlin J. Biliary tract cancers: understudied and poorly understood. J Clin Oncol 2015;33:1845-8.
4. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
5. Oh DY, He AR, Bouattour M, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. Lancet Gastroenterol Hepatol 2024;9:694-704.
6. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;401:1853-65.
7. Bartkowski R, Berger MR, Aguiar JL, et al. Experiments on the efficacy and toxicity of locoregional chemotherapy of liver tumors with 5-fluoro-2'-deoxyuridine (FUDR) and 5-fluorouracil (5-FU) in an animal model. J Cancer Res Clin Oncol 1986;111:42-6.
8. Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: Systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. Cancer 2016;122:758-65.
9. Wang X, Hu J, Cao G, et al. Phase II Study of Hepatic Arterial Infusion Chemotherapy with Oxaliplatin and 5-Fluorouracil for Advanced Perihilar Cholangiocarcinoma. Radiology 2017;283:580-9.
10. Cercek A, Boerner T, Tan BR, et al. Assessment of Hepatic Arterial Infusion of Floxuridine in Combination With Systemic Gemcitabine and Oxaliplatin in Patients With Unresectable Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncol 2020;6:60-7.
11. Zheng K, Wang X, Cao G, et al. Hepatic Arterial Infusion Chemotherapy with Oxaliplatin and 5-Fluorouracil for Advanced Gallbladder Cancer. Cardiovasc Intervent Radiol 2021;44:271-80.
12. Zhang L, Hao B, Geng Z, et al. Toripalimab: the First Domestic Anti-Tumor PD-1 Antibody in China. Front Immunol 2021;12:730666.

13. Wang ZX, Cui C, Yao J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. Cancer Cell 2022;40:277-288.e3.
14. Wang Z, Wu L, Li B, et al. Toripalimab Plus Chemotherapy for Patients With Treatment-Naive Advanced Non-Small-Cell Lung Cancer: A Multicenter Randomized Phase III Trial (CHOICE-01). J Clin Oncol 2023;41:651-63.
15. Mai HQ, Chen QY, Chen D, et al. Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomized Clinical Trial. JAMA 2023;330:1961-70.
16. Simone V, Brunetti O, Lupo L, et al. Targeting Angiogenesis in Biliary Tract Cancers: An Open Option. Int J Mol Sci 2017;18:418.
17. Gabrilovich D, Ishida T, Oyama T, et al. Vascular endothelial growth factor inhibits the development of dendritic cells and dramatically affects the differentiation of multiple hematopoietic lineages in vivo. Blood 1998;92:4150-66.
18. Allen E, Jabouille A, Rivera LB, et al. Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation. Sci Transl Med 2017;9:eaak9679.
19. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50. Erratum in: N Engl J Med 2007;356:318.
20. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study. J Clin Oncol 2023;41:3663-9.
21. El-Khoueiry AB, Ren Z, Chon H, et al. IMbrave151: A phase 2, randomized, double-blind, placebo-controlled study of atezolizumab with or without bevacizumab in combination with cisplatin plus gemcitabine in patients with untreated, advanced biliary tract cancer. J Clin Oncol 2023;41:491.
22. Hu J, Zhu X, Wang X, et al. Evaluation of percutaneous unilateral trans-femoral implantation of side-hole port-catheter system with coil only fixed-catheter-tip for hepatic arterial infusion chemotherapy. Cancer Imaging 2019;19:15.
23. Hildebrandt B, Pech M, Nicolaou A, et al. Interventionally implanted port catheter systems for hepatic arterial infusion of chemotherapy in patients with colorectal liver metastases: a Phase II-study and historical comparison with the surgical approach. BMC Cancer 2007;7:69.
24. Tanaka T, Arai Y, Inaba Y, et al. Radiologic placement of side-hole catheter with tip fixation for hepatic arterial infusion chemotherapy. J Vasc Interv Radiol 2003;14:63-8.
25. Arai Y, Takeuchi Y, Inaba Y, et al. Percutaneous catheter placement for hepatic arterial infusion chemotherapy. Tech Vasc Interv Radiol 2007;10:30-7.
26. Hodi FS, Ballinger M, Lyons B, et al. Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy. J Clin Oncol 2018;36:850-8.
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
28. Osada T, Chong G, Tansik R, et al. The effect of anti-VEGF therapy on immature myeloid cell and dendritic cells in cancer patients. Cancer Immunol Immunother 2008;57:1115-24.
29. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
30. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
31. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
32. de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res 2014;20:5384-91.
33. Longo V, Brunetti O, Azzariti A, et al. Strategies to Improve Cancer Immune Checkpoint Inhibitors Efficacy, Other Than Abscopal Effect: A Systematic Review. Cancers (Basel) 2019;11:539.
34. Yu H, Chen P, Cai X, et al. Efficacy and safety of PD-L1 inhibitors versus PD-1 inhibitors in first-line treatment with chemotherapy for extensive-stage small-cell lung cancer. Cancer Immunol Immunother 2022;71:637-44.
35. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021;398:27-40.
36. Shi GM, Huang XY, Wu D, et al. Toripalimab combined

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with lenvatinib and GEMOX is a promising regimen as first-line treatment for advanced intrahepatic cholangiocarcinoma: a single-center, single-arm, phase 2 study. Signal Transduct Target Ther 2023;8:106.
37. Sinn M, Nicolaou A, Gebauer B, et al. Hepatic arterial infusion with oxaliplatin and 5-FU/folinic acid for advanced biliary tract cancer: a phase II study. Dig Dis Sci 2013;58:2399-405.
38. Cai Z, He C, Zhao C, et al. Survival Comparisons of Hepatic Arterial Infusion Chemotherapy With mFOLFOX and Transarterial Chemoembolization in Patients With Unresectable Intrahepatic Cholangiocarcinoma. Front Oncol 2021;11:611118.
39. Limagne E, Thibaudin M, Nuttin L, et al. Trifluridine/Tipiracil plus Oxaliplatin Improves PD-1 Blockade in Colorectal Cancer by Inducing Immunogenic Cell Death and Depleting Macrophages. Cancer Immunol Res 2019;7:1958-69.
40. Liu WM, Fowler DW, Smith P, et al. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. Br J Cancer 2010;102:115-23.
41. Oh DY, Ruth He A, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022;1:EVIDoa2200015.
42. Jordan HA, Thomas SN. Novel proteomic technologies to address gaps in pre-clinical ovarian cancer biomarker discovery efforts. Expert Rev Proteomics 2023;20:439-50.
43. Gao M, Wu X, Jiao X, et al. Prognostic and predictive value of angiogenesis-associated serum proteins for immunotherapy in esophageal cancer. J Immunother Cancer 2024;12:e006616.
44. Thériault C, Pinard M, Comamala M, et al. MUC16 (CA125) regulates epithelial ovarian cancer cell growth, tumorigenesis and metastasis. Gynecol Oncol 2011;121:434-43.
45. Matsumoto K, Nakamura T. Hepatocyte growth factor and the Met system as a mediator of tumor-stromal interactions. Int J Cancer 2006;119:477-83.
46. Zhang X, Chen L, Dang WQ, et al. CCL8 secreted by tumor-associated macrophages promotes invasion and stemness of glioblastoma cells via ERK1/2 signaling. Lab Invest 2020;100:619-29.
47. Winkles JA, Tran NL, Berens ME. TWEAK and Fn14: new molecular targets for cancer therapy? Cancer Lett 2006;235:11-7.
48. Korbecki J, Grochans S, Gutowska I, et al. CC Chemokines in a Tumor: A Review of Pro-Cancer and Anti-Cancer Properties of Receptors CCR5, CCR6, CCR7, CCR8, CCR9, and CCR10 Ligands. Int J Mol Sci 2020;21:7619.
49. Wang X, Zeng Y, Ho DN, et al. Fibroblast Growth Factor-Inducible 14: Multiple Roles in Tumor Metastasis. Curr Mol Med 2015;15:892-904.
50. O'Connell J, O'Sullivan GC, Collins JK, et al. The Fas counterattack: Fas-mediated T cell killing by colon cancer cells expressing Fas ligand. J Exp Med 1996;184:1075-82.
51. Aharinejad S, Paulus P, Sioud M, et al. Colony-stimulating factor-1 blockade by antisense oligonucleotides and small interfering RNAs suppresses growth of human mammary tumor xenografts in mice. Cancer Res 2004;64:5378-84.
52. Teng Y, Fu X, Zhang Q, et al. Prognostic and clinicopathological significance of MMP12 in various cancers: a meta-analysis and bioinformatics analysis. Biomark Med 2023;17:623-34.

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