Original Article

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# mFOLFOX-HAIC+lenvatinib+PD-1 inhibitors versus GC/GS/GEMOX chemotherapy as a first line therapy for advanced biliary tract cancer: A single-center retrospective cohort study

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**SUMMARY** Biliary tract tumors (BTC) account for about 3% of all digestive system tumors, with rising incidence and limited treatment options, particularly for advanced stages, underscoring the need for innovative therapies. This retrospective cohort study evaluated the safety and efficacy of a novel regimen combining hepatic artery infusion chemotherapy with 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX-HAIC) alongside lenvatinib and programmed cell death protein-1 (PD-1) inhibitors (mFOLFOX-HAIC+lenvatinib+PD-1i) compared to standard regimens of gemcitabine plus cisplatin, gemcitabine plus S1, or gemcitabine plus oxaliplatin (GC/GS/GEMOX) in advanced BTC patients treated from March 2019 to November 2023. A total of 89 patients were analyzed, with 55 receiving hepatic arterial infusion chemotherapy and 34 receiving the GC/GS/GEMOX regimens. Among these, 23 patients were in the mFOLFOX-HAIC+lenvatinib+PD-1i group, while 24 were in the GC/GS/GEMOX group. The median progression-free survival (mPFS) for the mFOLFOX-HAIC+lenvatinib+PD-1i group was 15 months compared to 6 months for the GC/GS/GEMOX group. Similarly, the median overall survival (mOS) was 20 months for the mFOLFOX-HAIC+lenvatinib+PD-1i group versus 13 months for the GC/GS/GEMOX group. The objective response rate (ORR) and disease control rate (DCR) for the mFOLFOX-HAIC+lenvatinib+PD-1i group were 48.5% and 87.0%, respectively, both significantly higher than those observed in the GC/GS/GEMOX group at three months of treatment. The incidence of adverse events (AEs) was similar between the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group, at 86.5% and 84.2%, respectively, with no statistically significant difference in complication rates. Overall, mFOLFOX-HAIC+lenvatinib+PD-1i appears to be a safe and well-tolerated treatment for advanced BTC, demonstrating superior mPFS and mOS compared to standard regimens.

***Keywords*** advanced biliary tract cancer, hepatic arterial infusion chemotherapy (HAIC), programmed cell death protein-1 (PD-1), systemic chemotherapy

## 1. Introduction

Biliary tract cancer (BTC) is the second most common hepatic malignant tumor, accounting for approximately 2% of tumor-related deaths worldwide, with its incidence increasing annually (*1,2*). Surgical resection is considered the only potentially curative treatment. However, 70-80% of individuals are diagnosed at an advanced stage, rendering them ineligible for surgery. For the patients presenting with locally unresectable or distant metastatic disease, systemic therapy provides only a limited survival benefit of approximately 1 year, despite its ability to delay disease progression (*3*).

Biliary tract tumors are mainly supplied by hepatic arteries. Hepatic artery infusion chemotherapy (HAIC) is an effective treatment for BTC. It utilizes the hepatic arterial blood supply to deliver high-dose chemotherapy drug directly to the liver and tumor. Therefore, HAIC takes advantage of the liver's first-pass metabolism and provides liver-directed therapy while minimizing systemic exposure (*4*).

The mFOLFOX-HAIC+lenvatinib+PD-1 inhibitor

(mFOLFOX-HAIC+lenvatinib+PD-1i) treatment has shown good efficacy in the treatment of unresectable hepatocellular carcinoma in recent research conducted over the past two years (*5-7*). Additionally, This regimen has also been explored in clinical practice for advanced biliary tract cancers (*8,9*). The objective of this study is to compare the clinical outcomes of mFOLFOX-HAIC+lenvatinib+PD-1i versus systemic chemotherapy as first-line therapy for advanced BTC patients. The findings of this study may provide new insights into the treatment of advanced BTC and guide the development of future therapeutic strategies.

## 2. Materials and Methods

After the Institutional Review Board (IRB) of Beijing Tsinghua Changgung Hospital reviewed and approved the patient data analysis, medical records of patients with advanced BTC who underwent HAIC or GC/GS/GEMOX (gemcitabine+cisplatin/ gemcitabine+S1/ gemcitabine+oxaliplatin) chemotherapy at our center from March 2019 to November 2023 were reviewed. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and all participants provided informed consent prior to treatment.

### 2.1. Patient selection

Patient inclusion criteria for this study were as follows: (*i*) age between 18 and 80 years; (*ii*) diagnosis of advanced BTC confirmed by pathological findings, enhanced CT or MR results; (*iii*) advanced BTC, referred to unresectable due to vascular invasion or lymph node metastasis, assessed by our center's multidisciplinary team (MDT); (*iv*) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0-2 prior to undergoing GC/GS/GEMOX chemotherapy or mFOLFOX-HAIC; (*v*) Child-Pugh classification of A or B; (*vi*) hematological criteria: WBC $\geq 3.0\times10^9$/L, Hb $\geq$ 70g/L, PLT $\geq 75\times10^9$; (*vii*) liver function criteria: ALT and AST $\leq$ 5 times the upper limit of normal, serum bilirubin $\leq$ 3 times the upper limit of normal; (*viii*) renal function criteria: CCr $\leq$ 1.5 times the upper limit of normal or creatinine clearance rate $\geq$ 50ml/min; (*ix*) coagulation criteria: INR $\leq$ 2; (*x*) availability of complete follow-up data; and (*xi*) voluntary signing of informed consent.

Exclusion criteria for patients were as follows: (*i*) history of other malignant tumors; (*ii*) prior targeted therapy or immunotherapy before receiving GC/GS/GEMOX chemotherapy or mFOLFOX-HAIC; (*iii*) presence of severe cardiovascular disease; (*iv*) malignant hypertension; (*v*) Child-Pugh classification of C; (*vi*) chronic renal failure; (*vii*) presence of arteriovenous fistula in the liver; (*viii*) severe active infection; (*ix*) severe gastrointestinal bleeding within 6 weeks prior to treatment; (*x*) occurrence of severe thrombosis or thrombotic events within 6 months prior to treatment; and (*xi*) missing clinical data or non-compliance with follow-up.

All laboratory data and enhanced CT or MR images were collected within 1 month before initial treatment. The inclusion and exclusion process of this study was depicted in Figure 1, leading to the final inclusion of 89 patients.

### 2.2. Data collection

Clinical data were sourced from the electronic medical record system of Beijing Tsinghua Changgung

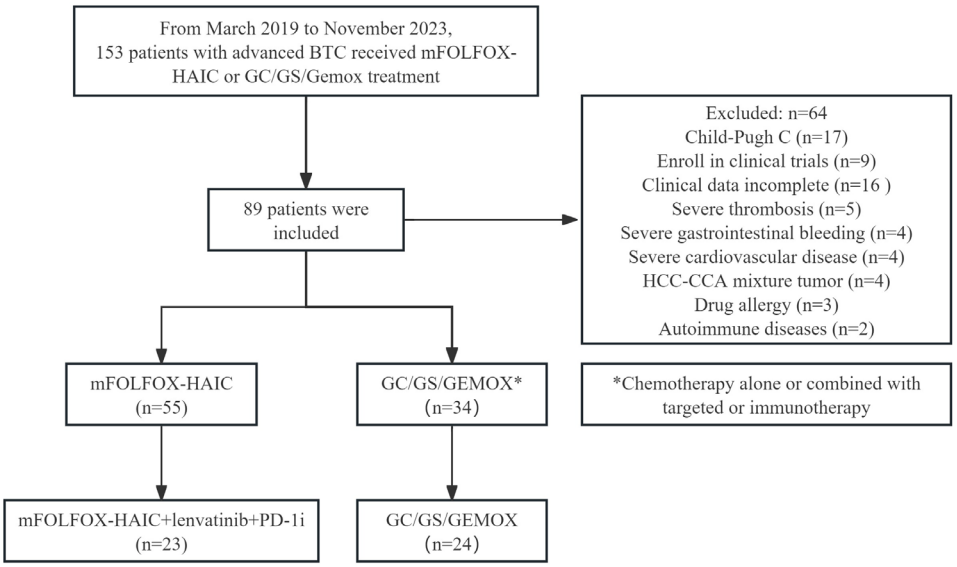


**Figure 1. Flow Diagram of Study Design.** HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; BTC, biliary tract caner; PD-1i, PD-1 inhibitors.

Hospital. The following parameters were collected and analyzed for the study: age, gender, comorbidities, HBV status, ECOG-PS score, white blood cell count (WBC), platelet count (PLT), serum albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), liver function classification (Child-Pugh score), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), protein induced by vitamin K absence II (PIVKA-II), presence of portal vein tumor thrombus, vascular invasion, distant metastases, and underwent percutaneous transhepatic cholangial drainage (PTCD).

### 2.3. Treatment Protocol

mFOLFOX-HAIC Group: Each HAIC treatment cycle lasted for 3 days. Digital subtraction angiography (DSA) was utilized for accurately select the tumor-feeding artery. To reduce the severity of gastrointestinal adverse reactions, gastric or gastroduodenal artery embolization was performed using spring coils. 5-Fluorouracil was administered continuously for 15 hours per day at a total dose of 1500 mg, while patients received 50 mg of oxaliplatin and 300 mg of calcium folinate every night for two hours. There was a 3 to 4-week or longer interval between two HAIC treatment cycles, and patients underwent 1 to 9 cycles of HAIC treatment. For patients with obstructive jaundice, PTCD drainage was performed, and HAIC was administered once the bilirubin level decreased to three times below the normal range.

GC/GS/GEMOX Group: GC: gemcitabine (1000 $mg/m^2$) and cisplatin (25 $mg/m^2$) intravenously on days 1 and 8. GS: Gemcitabine: 1000 $mg/m^2$ d1, 8 + S1: 80-120 $mg/m^2$, bid po d1-14. GEMOX: Gemcitabine: 1000 $mg/m^2$/d1, d8 + Oxaliplatin: 100 $mg/m^2$/dL. Each chemotherapy cycle was 3-4 weeks or longer due to the patient's intolerance. The patients received 2-10 cycles of chemotherapy. In the case of poor tolerance, some patients treated with GS regimen were changed to albumin paclitaxel combined with the S1 regimen according to the judgment of the attending physician.

PD-1 inhibitors (Tislelizumab, BeiGene Ltd, Beijing, China or Sintilimab, Innovent Biologics Ltd, Suzhou, China) were administered *via* intravenous drip in the duration of systemic chemotherapy or HAIC treatment, with a dose of 200 mg every 3-4 weeks.

Lenvatinib (Japan Eisai Co, Ltd) at a dosage of either 8 mg (≤ 60 kg) or 12 mg (> 60 kg) depending on their body weight. In cases of lenvatinib intolerance, dosage adjustment or discontinuation of the drug was necessary.

Each treatment was discontinued in the event of disease progression (PD), the patient being unable to tolerate toxic or adverse reactions, patient refusal of treatment or change of treatment regimen. Enhanced computed tomography (CT) or magnetic resonance imaging (MR) was performed, while follow-up visits were scheduled every 3 months.

### 2.4. Outcomes and assessments

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the duration from the commencement of the initial therapy till the occurrence of death owing to any cause or the last follow-up. PFS was referred to the duration from the beginning of the primary therapy till either the progression of the disease or the administration of bridging therapy and transplantation, or the last follow-up. Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was the standard methods employed by radiologists and hepatobiliary surgeons to assess the tumor response. The response criteria involved the determination of complete response (CR), partial response (PR), stable disease (SD), and PD. ORR was defined as the sum of CR and PR, whereas DCR was determined from the sum of CR, PR, and SD. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was utilized to evaluate treatment-related adverse events (AEs).

### 2.5. Statistical analysis

Baseline characteristics between the two groups were compared using Pearson's chi-square test, Fisher's exact test, or Wilcoxon rank sum test, as appropriate. Mean ± standard error (SE) was used to describe normally distributed variables, while median (interquartile range, IQR) was used for non-normally distributed variables. Kaplan-Meier method was employed for survival analysis, and log-rank test was used to assess differences in survival curves. Covariates with univariate $P < 0.05$ or those considered relevant to patient prognosis were included in multivariate Cox proportional hazards regression model, encompassing patients' basic information, treatment status, tumor status, and other factors to calculate hazard ratios (HR) and confidence intervals (CI). All descriptive and multivariate analyses were carried out using R software version 4.2.2. A two-tailed $P$-value < 0.05 was deemed statistically significant.

## 3. Results

### 3.1. Patient characteristics

From March 2019 to November 2023, a total of 89 patients with advanced BTC participated in this study. Of these, 55 patients received HAIC treatment, while the remaining 34 patients received GC/GS/GEMOX systemic chemotherapy (Chemotherapy alone or combined with targeted or immunotherapy). 23 patients (41.8%) in the HAIC group received lenvatinib+PD-1i (lenvatinib+PD-1 inhibitor) therapy and 24 patients

(70.6%) in the GC/GS/GEMOX (Chemotherapy alone or combined with targeted or immunotherapy) group received GC/GS/GEMOX chemotherapy alone. Patients in the HAIC group received a median of 4 cycles of HAIC, while patients in the GC/GS/GEMOX group received a median of 5 cycles of systemic chemotherapy. Table 1 displayed the demographic data and baseline characteristics of the two groups, which did not show significant differences in other clinical variables.

### 3.2. Survival

The median follow-up duration was 24 months (range 14.5-36 months), with the last follow-up conducted on July 28, 2024. There was no significant difference in PFS between HAIC group and GC/GS/GEMOX

**Table 1. Demographics of patients included in the study**

| Characteristic | HAIC (*n* = 55) | GC/GS/GEMOX* (*n* = 34) | *p*-value |
|---|---|---|---|
| Patient characteristics | | | |
| Age, median (IQR) | 65 (53, 68) | 62 (55, 71) | 0.752 |
| Sex, *n* (%) | | | 0.458 |
| Female | 20 (36.4%) | 16 (47.1%) | |
| Male | 35 (63.6%) | 18 (52.9%) | |
| Hepatitis, *n* (%) | | | 0.185 |
| Negative | 46 (83.6%) | 31 (91.3%) | |
| HBV | 9 (16.4%) | 3 (8.7%) | |
| Hypertension, *n* (%) | 17 (30.9%) | 16 (47.1%) | 0.301 |
| Diabetes mellitus, *n* (%) | 6 (10.9%) | 5 (14.7%) | 0.289 |
| Coronary artery disease, *n* (%) | 4 (7.3%) | 1 (2.9%) | 0.684 |
| Child-Pugh grade, *n* (%) | | | 0.785 |
| Grade A | 52 (94.5%) | 30 (88.2%) | |
| Grade B | 3 (5.5%) | 4 (11.8%) | |
| ECOG-PS, *n* (%) | | | < 0.001 |
| 0 | 4 (7.3%) | 14 (41.2%) | |
| ≥ 1 | 51 (92.7%) | 20 (58.8%) | |
| HAIC/chemotherapy times, median (IQR) | 4 (3, 5) | 5 (3, 7) | 0.006 |
| PTCD, *n* (%) | 26 (47.3%) | 14 (41.2%) | 0.583 |
| Tumor characteristics | | | |
| Size of largest nodule, median (IQR), mm | 48 (28, 67) | 42 (29, 61) | 0.353 |
| Tumor number, *n* (%) | | | 0.049 |
| Single | 2 (3.6%) | 5 (14.7%) | |
| Multiple | 52 (96.4%) | 29 (85.3%) | |
| Lymph node metastasis, *n* (%) | 28 (50.9%) | 22 (64.7%) | 0.329 |
| Extrahepatic metastasis, *n* (%) | 22 (40%) | 15 (44.1%) | 0.685 |
| Vascular invasion, *n* (%) | 45 (81.8%) | 22 (64.7%) | 0.062 |
| Thrombus, *n* (%) | | | 0.159 |
| Absent | 29 (52.7%) | 23 (67.6%) | |
| Portal vein thrombus | 26 (47.3%) | 11 (32.4%) | |
| PFS, median (IQR), months | 6 (2, 8) | 5 (2, 7) | 0.123 |
| OS, median (IQR), months | 15 (10, 18) | 12 (8, 15) | 0.243 |
| Laboratory test characteristics | | | |
| WBC, median (IQR), $\times10^9$/L | 6.25 (4.68, 8.23) | 5.98 (4.95, 7.96) | 0.421 |
| NEUT, median (IQR), $\times10^9$/L | 4.32 (3.08, 5.61) | 3.85 (3.23, 4.95) | 0.596 |
| LY, median (IQR), $\times10^9$/L | 1.31 (0.91, 1.72) | 1.26 (1.12, 1.68) | 0.651 |
| Hb, mean ± SD, g/L | 115.89 ± 19.512 | 121.85 ± 20.865 | 0.578 |
| PLT, median (IQR), $\times10^9$/L | 201 (134, 252) | 216 (168, 263) | 0.845 |
| ALB, median (IQR), g/L | 38.4 (38.2, 10.8) | 40.1 (35.3, 44.8) | 0.063 |
| AST, median (IQR), U/L | 39.7 (25.8, 55.7) | 24.6 (17.3, 43.9) | 0.065 |
| ALT, median (IQR), U/L | 32 (22.8, 51.5) | 25.2 (16.1, 54.2) | 0.146 |
| ALP, median (IQR), U/L | 168 (118, 361) | 109 (89, 205) | 0.061 |
| GGT, median (IQR), U/L | 129 (71, 261) | 121 (53, 221) | 0.062 |
| CHE, mean ± SD, U/L | 4896 ± 1652 | 5263 ± 1394 | 0.087 |
| TBIL, median (IQR), μmol/L | 22.5 (12.6, 56.4) | 19.8 (12.8, 26.9) | 0.048 |
| AFP, median (IQR), ng/mL | 4.20 (2.31, 4.31) | 4.32 (2.44, 5.85) | 0.695 |
| CEA, median (IQR), μg/L | 3.28 (1.95, 5.63) | 2.87 (2.25, 4.89) | 0.924 |
| CA19-9, median (IQR), U/mL | 116.8 (19.6, 1052.6) | 141.2 (29.6, 1186) | 0.296 |
| PIVKA-II, median (IQR), mAU/mL | 28.3 (19.5, 68.52) | 24.97 (19.9, 51.3) | 0.601 |

HAIC, hepatic artery infusion chemotherapy; IQR, interquartile range; HBV, hepatitis B virus; PTCD, percutaneous transhepatic cholangial drainage; WBC, white blood cell; NEUT, neutrophil; LY, lymphocyte; Hb, hemoglobin; SD, standard deviation; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CHE, cholinesterase; TBIL, total bilirubin; AFP, alpha-Fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PIVKA-II, protein induced by vitamin K absence II. *GC/GS/GEMOX (Chemotherapy alone or combined with targeted or immunotherapy)

group after logistic rank sum test (HR = 0.824; 95% CI 0.501-1.210; $P$ = 0.330) (Figure 2A), as was OS (HR = 0.781; 95% CI 0.465-1.331; $P$ = 0.297) (Figure 2B). As shown in Table 1, the median progression-free survival (mPFS) of HAIC group and GC/GS/GEMOX group were 6 months (95% CI 3.748-8.541) and 5 months (95% CI 2.501-7.412), respectively. The median overall survival (mOS) for the two groups were 15 months and 12 months, respectively. There were no significant differences in mPFS and mOS between the two groups ($P$ = 0.324 and $P$= 0.875, respectively).

### 3.3. Impact of lenvatinib and PD-1 inhibitors on the outcomes

23 patients (41.8%) in the HAIC group received lenvatinib and PD-1i (mFOLFOX-HAIC+lenvatinib+PD-1i) and 24 patients (70.6%) in the GC/GS/GEMOX group only received chemotherapy without targeted or immunotherapy ($P$ = 0.001). Table 2 shows the demographic data and baseline characteristics of the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group. There was no significant difference in clinical variables between the two groups except for the ECOG-PS score. ECOG-PS score in the GC/GS/GEMOX group was better than in the mFOLFOX-HAIC+lenvatinib+PD-1i group. The patients in the mFOLFOX-HAIC+lenvatinib+PD-1i group had significantly better PFS (HR = 0.475; 95% CI 0.195 - 0.841; $P$ = 0.004; Figure 3A) and OS (HR = 0.374; 95% CI 0.181 - 0.851; $P$ = 0.002; Figure 3B) than those in the GC/GS/GEMOX group. The mPFS of the mFOLFOX-HAIC+lenvatinib+PD-1i group and GC/GS/GEMOX group were 15 months (95% CI 7.147-24.732) and 6 months (95% CI 2.684-7.875), respectively. The mOS in the mFOLFOX-HAIC+lenvatinib+PD-1i group was 20 months, significantly longer than 13 months observed in the GC/GS/GEMOX group ($P$ < 0.05).

### 3.4. Tumor response

Treatment response was evaluated in mRECIST criteria at the 3rd-month. The result showed that 3 (13.1%) patients in the mFOLFOX-HAIC+lenvatinib+PD-1i group had PD, 10 (43.5%) patients showed SD, 8 (34.8%) patients achieved PR, and 2 (8.6%) patient achieved CR, resulting in an ORR of 43.5% and DCR of 87.0%. 2 patients who achieved CR underwent surgical resection. The pathology showed necrotic tissue with no tumor cells found. In the GC/GS/GEMOX group, 9 (37.5%) patients had PD, 9 (37.5%) patients had SD, and 6 (25.0%) patients achieved PR; however, no patient achieved CR. The ORR and DCR were 25% and 62.5%, respectively. The mFOLFOX-HAIC+lenvatinib+PD-1i group showed a higher ORR and DCR than the GC/GS/GEMOX group (Table 3).

### 3.5. Safety and tolerability

As shown in Table 4, based on the CTCAE 5.0 standards, the incidence of AEs for the mFOLFOX-HAIC+lenvatinib+PD-1i group and the GC/GS/GEMOX group were 91.3% and 87.5%, respectively. In the HAIC group, the most common grade 1-2 AEs were hypertension (78.2%), nausea (78.2%), and fatigue (78.2%) , and the most common grade 3-4 AE was hypertension (47.9%). In the GC/GS/GEMOX group, the most common grade 1-2 AEs were vomiting (75.0%), fatigue (75.0%) and nausea (66.7%), and the most common grade 3-4 AE was leukopenia (13.0%). In terms of grade 1-2 AEs, the incidence of hypertension, hypothyroidism and elevated transaminase levels in

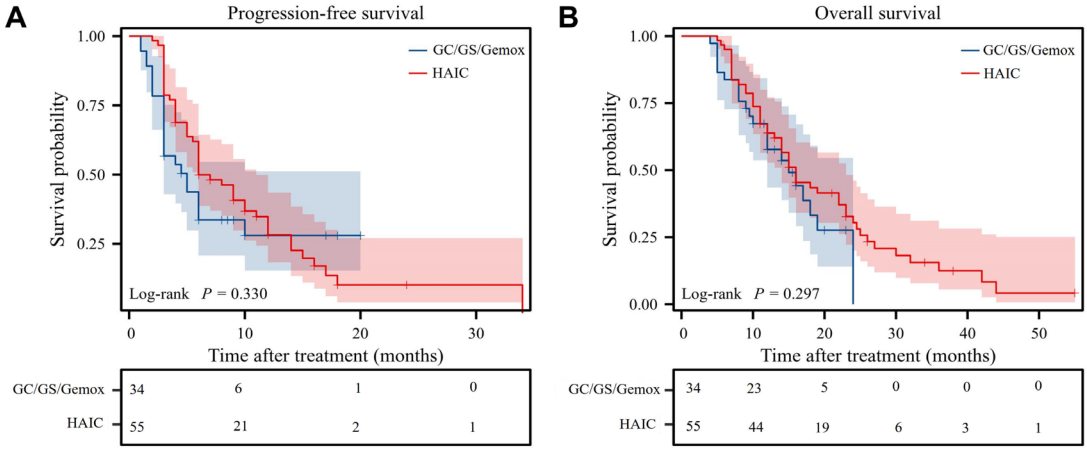


**Figure 2. Kaplan-Meier Survival Survival Analysis for HAIC *vs.* GC/GS/GEMOX.** Kaplan-Meier analysis of progression-free survival (PFS) and overall survival (OS) in advanced biliary tract cancer patients treated with HAIC versus GC/GS/GEMOX regimens (Chemotherapy alone or combined with targeted or immunotherapy). Panel A details PFS, and Panel B details OS. The curves indicate no significant difference in survival between the two treatment groups, suggesting similar efficacy for both therapeutic strategies. HAIC, hepatic arterial infusion chemotherapy; PFS, progression-free survival; OS, overall survival.

**Table 2. Demographic data of the patients who had received PD-1 inhibitors therapy in the study**

| Characteristic | mFOLFOX-HAIC+lenvatinib+PD-1i (*n* = 23) | GC/GS/GEMOX* (*n* = 24) | *p*-value |
|---|---|---|---|
| Patient characteristics | | | |
| Age, median (IQR) | 62 (52, 67) | 64 (56, 72) | 0.585 |
| Sex, *n* (%) | | | 0.386 |
| Female | 7 (30.4%) | 11 (45.8%) | |
| Male | 16 (69.6%) | 13 (54.2%) | |
| Hepatitis, *n* (%) | | | 0.375 |
| Negative | 20 (87.0%) | 22 (91.7%) | |
| HBV | 6 (13.0%) | 2 (8.3%) | |
| Hypertension, *n* (%) | 11 (47.8%) | 12 (50%) | 0.789 |
| Diabetes mellitus, *n* (%) | 3 (13.0%) | 4 (16.7%) | 1.023 |
| Coronary artery disease, *n* (%) | 3 (13.0%) | 2 (8.3%) | 0.989 |
| Child-Pugh grade, *n* (%) | | | 1.045 |
| Grade A | 21 (91.3%) | 21 (87.5%) | |
| Grade B | 2 (8.7%) | 3 (12.5%) | |
| ECOG-PS, *n* (%) | | | < 0.001 |
| 0 | 1 (4.3%) | 11 (45.8%) | |
| ≥ 1 | 22 (95.7%) | 13 (54.2%) | |
| HAIC/chemotherapy times, median (IQR) | 4.12 ± 1.71 | 4.89 ± 1.28 | 0.032 |
| PTCD, *n* (%) | 11 (47.8%) | 11 (45.8%) | 0.574 |
| Tumor characteristics | | | |
| Size of largest nodule, median (IQR), mm | 52.8 ± 28.6 | 49.2 ± 26.1 | 0.561 |
| Tumor number, *n* (%) | | | 0.141 |
| Single | 2 (8.8%) | 2 (8.4%) | |
| Multiple | 21 (91.2%) | 22 (91.6%) | |
| Vascular invasion, *n* (%) | 18 (75.3%) | 16 (63.4%) | 0.125 |
| Lymph node metastasis, *n* (%) | 15 (62.8%) | 17 (60.7%) | 0.814 |
| Extrahepatic metastasis, *n* (%) | 9 (34.6%) | 11 (46.3%) | 0.634 |
| Thrombus, *n* (%) | | | 0.192 |
| Absent | 12 (54.8%) | 18 (66.7%) | |
| Portal vein thrombus | 11 (43.2%) | 6 (33.3%) | |
| Laboratory test characteristics | | | |
| WBC, median (IQR), $\times 10^9$/L | 6.12 (4.32, 7.85) | 5.89 (4.96, 7.62) | 0.561 |
| NEUT, median (IQR) , $\times 10^9$/L | 3.96 (3.13, 5.65) | 3.71 (3.25, 6.85) | 0.451 |
| LY, median (IQR) , $\times 10^9$/L | 1.09 (0.91, 1.71) | 1.12 (1.09, 1.68) | 0.712 |
| Hb, mean ± SD, g/L | 118 ± 23.01 | 119.5 ± 20.13 | 0.875 |
| PLT, median (IQR) , $\times 10^9$/L | 184.8 (142, 239) | 210.5 (167, 252) | 0.301 |
| ALB, mean ± SD, g/L | 39.12 ± 2.58 | 40.12 ± 4.59 | 0.125 |
| AST, median (IQR), U/L | 39.5 (27.25, 61.78) | 32.4 (18.45, 46.78) | 0.145 |
| ALT, median (IQR), U/L | 34.1 (24, 64.14) | 29.8 (15.11, 56.04) | 0.198 |
| ALP, median (IQR), U/L | 191 (107.4, 359.4) | 125.2 (89.3, 241.1) | 0.371 |
| GGT, median (IQR), U/L | 170 (58.95, 256.85) | 105 (37.8, 196.32) | 0.091 |
| CHE, median (IQR), U/L | 4796.3 (3543.1, 6041.5) | 5344.8 (4528.2, 6351.8) | 0.148 |
| TBIL, median (IQR), μmol/L | 24.84 (13.1, 54.3) | 16.03 (10.45, 29.41) | 0.157 |
| AFP, median (IQR), ng/mL | 3.21 (2.12, 3.95) | 3.41 (2.91, 5.442) | 0.085 |
| CEA, median (IQR), μg/L | 3.65 (2.18, 5.93) | 2.41 (2.12, 3.98) | 0.506 |
| CA19-9, median (IQR), U/mL | 57.10 (9.22, 758.7) | 156.47 (43.12, 1181.6) | 0.095 |
| PIVKA-II, median (IQR), mAU/mL | 35.62 (25.40, 212.52) | 24.02 (20.07, 73.48) | 0.394 |

HAIC, hepatic artery infusion chemotherapy; PD-1i, Programmed Death 1 inhibitor; IQR, interquartile range; HBV, hepatitis B virus; PTCD, percutaneous transhepatic cholangial drainage; WBC, white blood cell; NEUT, neutrophil; LY, lymphocyte; Hb, hemoglobin; SD, standard deviation; PLT, blood platelet; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CHE, cholinesterase; TBIL, total bilirubin; AFP, alpha-Fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; PIVKA-II, protein induced by vitamin K absence II.GC/GS/Gemox*: only chemotherapy.

the mFOLFOX-HAIC+lenvatinib+PD-1i group was significantly higher than that in the GC/GS/GEMOX group ($P < 0.05$). The incidence of hypertension and leukopenia in grade 3-4 AEs was significantly different between the two groups. No grade 5 AEs were observed in either group.

## 4. Discussion

BTC includes Gall bladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC) and perihilar cholangiocarcinoma (PHCC). They are usually diagnosed in locally advanced or node-positive stage, with a short survival rate (*3,10-14*). BTC is prone to recurrence and metastasis after surgery. The treatment of BTC is a nationwide challenge. This is the first clinical study comparing the efficacy and safety of mFOLFOX-HAIC+lenvatinib+PD-1i with systemic chemotherapy (GC/GS/GEMOX) as first-line therapies for advanced BTC. Our findings indicated that

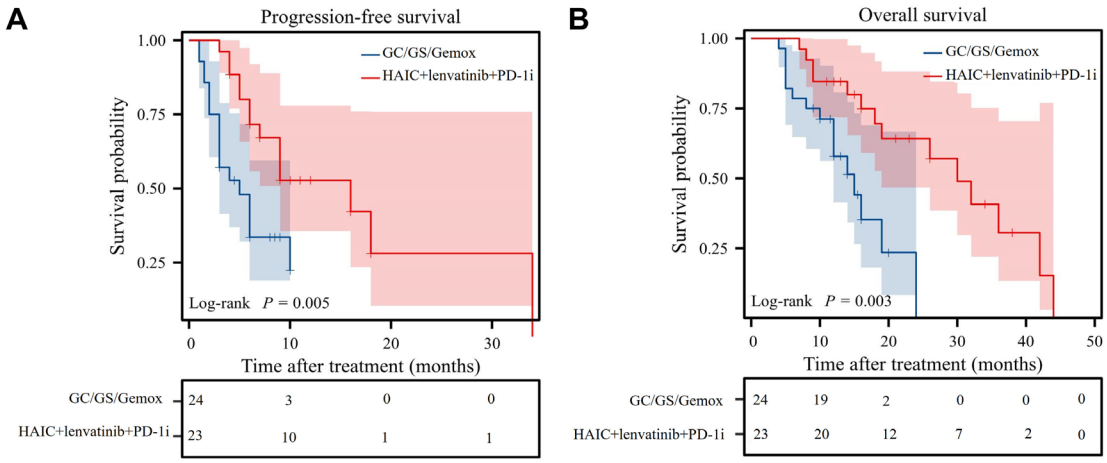


**Figure 3. Kaplan-Meier Survival Analysis for mFOLFOX-HAIC+lenvatinib+PD-1i *vs.* GC/GS/GEMOX.** The Kaplan-Meier survival curves (Panel A and B) compare progression-free survival and overall survival respectively, between patients receiving mFOLFOX-HAIC+lenvatinib+PD-1i and those treated with the GC/GS/GEMOX regimen. The curves suggest improved life expectancy for the HAIC +lenvatinib+PD-1i group. HAIC, hepatic arterial infusion chemotherapy; PD-1i, PD-1 inhibitors; HR, harzard ratio.

**Table 3. Tumor response rates between the two groups at the third month of the treatment**

| | mFOLFOX-HAIC+lenvatinib+PD1i ($n$ = 23) | GC/GS/GEMOX* ($n$ = 24) | $p$-value |
|---|---|---|---|
| Tumor response, $n$ (%) | | | |
| CR | 2 (8.6%) | 0 (0%) | 0.745 |
| PR | 8 (34.8%) | 6 (25.0%) | 0.785 |
| SD | 10 (43.5%) | 9 (37.5%) | 0.712 |
| PD | 3 (13.1%) | 9 (37.5%) | 0.412 |
| ORR | 10 (43.5%) | 6 (25.0%) | 0.528 |
| DCR | 20 (87.0%) | 15 (62.5%) | 0.378 |
| PFS, median (IQR), months | 15 (4, 20) | 6 (3, 9) | 0.002 |
| OS, median (IQR), months | 20 (10, 23) | 13 (9, 16) | 0.029 |

HAIC, hepatic artery infusion chemotherapy; 95% CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. GC/GS/GEMOX*: only chemotherapy.

**Table 4. The adverse events in the two groups according to Common Terminology Criteria for Adverse Events version 5.0**

| | Grade 1-2 AEs | | | Grade 3-4 AEs | | |
|---|---|---|---|---|---|---|
| $n$ (%) | mFOLFOX-HAIC+ lenvatinb+PD-1i ($n$ = 23) | GC/GS/ GEMOX ($n$ = 24) | $p$ value | mFOLFOX-HAIC+ lenvatinb+PD-1i ($n$ = 23) | GC/GS/ GEMOX ($n$ = 24) | $p$ value |
| Nausea | 18 (78.2%) | 16 (66.7%) | 0.064 | 0 (0) | 2 (8.3%) | - |
| Vomiting | 15 (65.2%) | 18 (75.0%) | 0.162 | 0 (0) | 0 (0) | - |
| Abdominal pain | 13 (56.5%) | 9 (39.1%) | 0.075 | 0 (0) | 1 (4.2%) | 0.140 |
| Abdominal distention | 6 (26.1%) | 5 (21.7%) | 0.408 | 0 (0) | 0 (0) | - |
| Diarrhea | 12 (52.1%) | 6 (16.2%) | 0.668 | 1 (4.3%) | 1 (4.2%) | 0.631 |
| Fever | 10 (43.5%) | 13 (46.4%) | 0.521 | 2 (8.7%) | 0 (0) | 0.288 |
| Hypertension | 18 (78.2%) | 6 (26.1%) | 0.021* | 11 (47.9%) | 1 (4.2%) | 0.015* |
| Hand-foot syndrome | 7 (30.4%) | 9 (39.1%) | 0.449 | 2 (8.7%) | 1 (4.2%) | 0.116 |
| Gastric mucosal bleeding | 2 (8.7%) | 5 (21.7%) | 0.223 | 1 (4.3%) | 1 (4.2%) | 0.915 |
| Joint pain | 1 (4.3%) | 5 (21.7%) | 0.059 | 0 (0) | 0 (0) | - |
| Fatigue | 18 (78.2%) | 18 (75.0%) | 0.114 | 1 (4.3%) | 1 (4.2%) | 0.915 |
| Infection | 4 (17.4%) | 3 (13.0%) | 0.640 | 1 (4.3%) | 1 (4.2%) | 0.631 |
| Thrombocytopenia | 14 (60.9%) | 11 (47.8%) | 0.193 | 1 (4.3%) | 2 (8.7%) | 0.915 |
| Leukopenia | 8 (34.8%) | 9 (39.1%) | 0.645 | 1 (4.3%) | 3 (13.0%) | 0.035* |
| Elevated transaminases | 15 (65.2%) | 7 (30.4%) | 0.001* | 1 (4.3%) | 1 (4.2) | 0.525 |
| Elevated bilirubin | 6 (26.1%) | 3 (13.0%) | 0.217 | 1 (4.3%) | 0 (0) | 0.288 |
| Immune-mediated pneumonia | 0 (0) | 0 (0) | - | 1 (4.3%) | 0 (0) | 0.525 |
| Hypothyroidism | 3 (13.0%) | 0 (0) | 0.015* | 1 (4.3%) | 0 (0) | 0.525 |
| Immune-mediated myocarditis | 0 (0) | 0 (0) | - | 1 (4.3%) | 0 (0) | 0.525 |

AEs, adverse events; HAIC, hepatic artery infusion chemotherapy; GC/GS/Gemox: only chemotherapy. *Denotes a $p$-value < 0.05.

mFOLFOX-HAIC+lenvatinib+PD-1i improved survival rates in advanced BTC patients compared to systemic chemotherapy. Especially two patients who underwent mFOLFOX-HAIC+lenvatinib+PD-1i achieved CR and successfully underwent surgical treatment. Although mFOLFOX-HAIC+lenvatinib+PD-1i resulted in a higher incidence of grade 1-2 AEs, such as hypertension and elevated transaminase levels compared to systemic chemotherapy. HAIC did not lead to a higher incidence of grade 3-4 AEs or grade 5 AEs. All AEs could be resolved by effective interventions. These findings represent a potential paradigm shift in advanced BTC treatment. mFOLFOX-HAIC+lenvatinib+PD-1i has the potential to be a safe and effective alternative for first-line treatment for advanced biliary tract cancer.

While doublet chemotherapy with gemcitabine and cisplatin has been regarded as the most effective first-line treatment for the past decade (*3*), its efficacy is often hindered by systemic toxicity, limited drug delivery to the tumor site, and the development of drug resistance. The efficacy of systemic chemotherapy alone remains limited, and there is an urgent need for alternative treatment approaches. Gonzalez-Carmona *et al*. (*15*) demonstrated that the combination of local radiation therapy combined with gemcitabine and cisplatin chemotherapy significantly prolonged survival compared to chemotherapy alone in patients with advanced BTC. Furthermore, this combination therapy was well-tolerated, indicating good tolerability. Edeline *et al*. (*16*) combined selective internal radiotherapy (SIRT) with chemotherapy (gemcitabine and cisplatin) as first-line treatment for unresectable BTC. This regime achieved downstaging and transfer to surgery in 22% of patients.

BTC is often mainly supplied by the hepatic artery. HAIC utilizes the hepatic arterial blood supply to deliver high-dose chemotherapeutics directly to the liver including the tumor. Therefore, HAIC takes advantage of the liver's first-pass metabolism and provides liver-directed therapy while minimizing systemic exposure (*4*). HAIC have the potential to achieve comparable or even superior survival outcomes compared to systemic chemotherapy alone. Konstantinidis *et al*. (*12*) compared the outcomes of patients with unresectable BTC who received HAIC in addition to systemic chemotherapy with those who received systemic chemotherapy alone. The combination of systemic chemotherapy and HAIC improved the survival compared to systemic chemotherapy alone (30.8 vs 18.4 months). Cercek *et al*. (*11*) treated unresectable BTC patients with the HAIC in combination with systemic gemcitabine and oxaliplatin. The authors reported a mPFS of 11.8 months, a 6-month PFS rate of 84.1%, a mOS of 25.0 months, and a 1-year OS rate of 89.5%. In a study conducted by Ishii *et al*. (*17*), patients underwent HAIC with gemcitabine, cisplatin, and 5-fluorouracil were compared to those who underwent systemic gemcitabine and cisplatin treatment. The OS of the HAIC group was superior to that of the standard chemotherapy cohort, as it demonstrated a favorable response and disease control in patients who had previously shown intolerance to the gemcitabine plus cisplatin combination therapy. Wang *et al*. (*18*) conducted a prospective phase II study, showing that HAIC with oxaliplatin and 5-fluorouracil is a promising treatment option for advanced BTC. The study demonstrated notable efficacy in terms of tumor control, with an ORR of 67.6% and a DCR of 89.2%, and exhibited a survival benefit with median PFS, local PFS, and OS of 12.2, 25.0, and 20.5 months, respectively. HAIC could potentially serve as an effective therapeutic alternative for individuals with advanced BTC.

PD-1 inhibitors have emerged as a promising treatment modality in various malignancies by enhancing the immune response against cancer cells through the blockade of the PD-1/PD-L1 interaction. PD-L1 is expressed in approximately half of the BTC patients, which is associated with poor prognosis (*19*). A multicenter phase II study involving 54 patients evaluated the efficacy and safety of nivolumab for advanced BTC patients who had undergone prior treatment (*20*). The study reported an ORR of 22% and a DCR of 59%. Furthermore, the mPFS and mOS were 3.68 months and 14.24 months, respectively. Notably, all patients who responded to treatment exhibited positive PD-L1 expression in their tumors, which was associated with longer PFS. Similarly, a retrospective multicenter study assessed the clinical efficacy and safety of pembrolizumab in GC chemotherapy-refractory BTC patients (*21*). In this study, 51 advanced BTC patients with PD-L1-positive tumors after progressing on first-line GC treatment received pembrolizumab. The ORR was 9.8%, with a mPFS of 2.1 months and a mOS of 6.9 months. Grade 3/4 AEs occurred in only 4 patients (7.8%). Another phase I study evaluated the safety and tolerability of durvalumab (anti-PD-L1 antibody) and tremelimumab (anti-CTLA-4 antibody) in advanced BTC patients who experienced chemotherapy failure (*22*). The mPFS and mOS were 8.1 months and 10.1 months, respectively. This study demonstrated that durvalumab plus tremelimumab combination therapy were well-tolerated and showed promising clinical efficacy. The ORR and DCR of advanced BTC patients treated with PD-1 inhibitors reported by Ye *et al*. (*23*) were 16.7% and 79.6%, respectively, and the mPFS and mOS were 6.6 months and 13.9 months. Deng *et al*. (*24*) reported that treated with PD-1 inhibitors, the mOS, mPFS, and median time to progression (mTTP) of patients with advanced BTC were 19.3 months, 11.6 months, and 11.6 months, respectively, with an ORR of 23.8% and a DCR of 85.7%.

Although immune checkpoint inhibitors (ICIs) alone exhibit limited efficacy, their combination with chemotherapy or radiotherapy has demonstrated

favorable responses in BTC (*25*). The groundbreaking Topaz-1 trial marked the inaugural global phase III study investigating the use of first-line durvalumab in combination with GC chemotheray for advanced BTC treatment (*26*). The results demonstrated a significant improvement in both OS and PFS in the durvalumab plus GC group compared to the placebo plus GC group. Lei *et al*. (*27*) conducted a study comparing the survival outcomes of patients from 22 centers in China and found that the combination of chemotherapy and PD-1 inhibitors provided greater survival benefits than chemotherapy alone. The mPFS was 6.3 months in the combination therapy group compared to 3.8 months in the chemotherapy alone group, and the mOS was 10.7 months in the combination therapy group compared to 9.3 months in the chemotherapy alone group. Gou *et al*. (*28*) conducted a comparative study in advanced BTC patients receiving combination therapy of chemotherapy and PD-1 inhibitors versus chemotherapy alone. The study findings revealed that the addition of PD-1 inhibitors did not significantly improve the ORR and DCR, but it significantly prolonged the PFS.

Researches have shown that targeted therapy, immunotherapy, and conventional chemotherapy in BTC have certain mechanistic links, and the combination of those can improve the prognosis of advanced BTC patients (*19*). Huang *et al*. (*29*) conducted a comparison analysis of first-line treatments for patients with advanced BTC, specifically PD-1/PD-L1 inhibitors plus lenvatinib or gemcitabine/cisplatin (GC). The study reported that patients in the PD-1/PD-L1 inhibitors plus lenvatinib group were more likely to have an Eastern Cooperative Oncology Group (ECOG) performance status value above 1or have ascites. The response rate (RR) was 16.0% in the PD-1/PD-L1 inhibitors plus lenvatinib group compared to 23.1% in the GC group ($P$ = 0.777). The DCR was 52.0% in the PD-1/PD-L1i+lenvatinib group compared to 46.2% in the GC group ($P$ = 0.676). The combination therapy of PD-1/PD-L1 inhibitors plus lenvatinib was associated with a longer PFS compared to the GC group; however, this difference did not reach statistical significance (lenvatinib: 9.5 months, GC: 5.1 months, $P$ = 0.454). Therefore, both PD-1/PD-L1 inhibitors in combination with lenvatinib or GC demonstrated significant efficacy and safety as first-line treatment options for patients with advanced intrahepatic BTC. For patients who refuse or are intolerant to chemotherapy, PD-1/PD-L1 inhibitors plus lenvatinib would be a recommended choice. Xie *et al*. (*30*) administered lenvatinib plus PD-1 inhibitor to patients with chemotherapy-refractory advanced BTC. The mPFS was 5.83 ± 0.76 months. The 3-month and 6-month PFS rates were 80.0% and 32.5%, respectively. The mOS was 14.30 ± 1.30 months. The 12-month and 18-month survival rates were 61.4% and 34.7%, respectively. The ORR was 17.5%, and the DCR was 75.0%. According to a multicenter retrospective real-world study, the combination of PD-1 inhibitors, lenvatinib, and Gemox chemotherapy demonstrated efficacy and tolerability as a treatment regimen for advanced BTC (*31*). Shi *et al*. (*32*) demonstrated that toripalimab in combination with lenvatinib and Gemox showed promise as a first-line regimen for treating advanced BTC, with a mOS of 22.5 months, mPFS of 10.2 months, median duration of response (mDoR) of 11.0 months, and a DCR of 93.3%. Wang *et al*. (*33*) reported that the adding radiotherapy (RT) to toripalimab and lenvatinib may enhance the efficacy for advanced BTC patients. The combination of toripalimab and lenvatinib with RT demonstrated a favorable safety profile, with no significant increase in specific toxicities. Zhu *et al*. (*34*) conducted a retrospective study of patients with advanced BTC who received lenvatinib combined with PD-1/PD-L1 inhibitors plus gemcitabine and oxaliplatin (Gemox) chemotherapy. The study showed a mOS of 13.4 months and a mPFS of 9.27 months. The ORR, DCR, and clinical benefit rate were reported as 43.9%, 91.2%, and 73.7%, respectively. Zhang *et al*. (*35*) discovered that advanced BTC patients who experienced immune-related adverse events (irAEs) following PD-1 inhibitor combination therapy had a higher DCR compared to patients who did not experience irAEs (90.6% *vs.* 70.4%). Additionally, these patients exhibited superior mOS and mPFS compared to those who did not experience irAEs (mOS: 21.2 months *vs.* 10.0 months; mPFS: 9.0 months *vs.* 4.4 months). Notably, Wei *et al*. have provided preliminary evidence demonstrating the safety, tolerability, and potential survival benefits of combined treatment with HAIC, lenvatinib, and PD-1 inhibitors in advanced BTC patients (*8*).

This study had certain limitations. First, its retrospective design limited the analysis to preexisting data, which made the analysis susceptible to potential biases and variations in data collection. Second, the relatively small sample size might have increased the likelihood of findings, and thus, the results should be interpreted with caution.

In conclusion, our study suggested that HAIC in combination with lenvatinib and PD-1 inhibitors has the potential to serve as a safe and effective alternative for first-line treatment of advanced BTC. These findings determined the importance of further research and prospective studies to validate these results and optimize treatment strategies for advanced BTC patients.

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