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Hepatic artery infusion chemotherapy plus an immune checkpoint inhibitor and lenvatinib for the treatment of biliary tract carcinoma

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Abstract

Background The prognosis is still dismal, although several tyrosine kinase inhibitors (TKIs) with/without immune checkpoint inhibitors (ICIs) have shown promising results in the treatment of biliary tract carcinoma (BTC). However, the combination of hepatic artery infusion chemotherapy (HAIC) with ICIs and TKIs may have potential in patients with BTC, according to the success of such a regimen for hepatocellular carcinoma. Hence, this study aimed to evaluate the preliminary efficacy and safety profile of combination therapy with HAIC plus ICI and lenvatinib in BTC patients.

Methods This retrospective study included all BTC patients histologically diagnosed with combination therapy, which included HAIC with Gemox (Gemox-HAIC), programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitor, and lenvatinib from July 2021 to October 2023. The outcomes were the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profile.

Results The median follow-up period was 7.0 months (range: 1.0–28.0 months). The ORR and DCR were 72.7% and 90.9%, respectively, with 0.0% CR, 72.7% PR, 18.2% SD, and 9.1% PD. The median PFS was 6.1 (4.3–8.0 (95% CI) months, and the 12-month accumulating PFS rate was 26.0%. The median OS was 10.3 (8.1–12.5 (95% CI) months, and the 12-month accumulating OS rate was 43.2%. The major adverse events included leukopenia (22.7%), thrombocytopenia (22.7%), vomiting (9.1%), etc. All AEs were grade 1–2 except for grade 3–4 leukopenia and 3–4 thrombocytopenia in one patient.

Conclusion The combination therapy of Gemox-HAIC with ICIs and lenvatinib shows promising efficacy and tolerable safety profiles in BTC patients.

Keywords Hepatic artery infusion chemotherapy, Immune checkpoint inhibitor, Biliary tract carcinoma, Treatment efficacy, Safety profile

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Introduction

Biliary tract carcinomas (BTCs) include intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC). BTC is a rare but highly aggressive malignancy that accounts for less than 1% of all cancers worldwide [1, 2]. Owing to its insidious onset, 60-70% of BTC patients are diagnosed at an advanced stage and are thus ineligible for surgical resection. Systemic chemotherapy is the standard approach for patients with advanced BTC. The common first-line regimens include two different treatments or plans of medicine: gemcitabine combined with cisplatin (GemCis) and gemcitabine combined with oxaliplatin (Gemox) [3]. However, more effective therapies are still needed to further improve BTC management.

Some significant efforts have been made to explore novel treatments for BTC [4]. The immune checkpoint inhibitor (ICI) reduces immune evasion and tolerance by activating cytotoxic T cells, which achieves better efficacy in combination with chemotherapy in BTC patients [5–8]. Tyrosine kinase inhibitors (TKIs) are another potential option for BTC management because they inhibit cancer cell proliferation, which shows specific efficacy in combination with or without ICIs in BTC patients [4, 9–13].

Hepatic artery infusion chemotherapy (HAIC) is a treatment that directly delivers chemotherapeutic agents into the liver via the percutaneous catheterization of feeding arteries [14]. This intervention reduces the systemic diffusion of drugs and provides a higher concentration of chemotherapeutic agents in the tumor, which results in greater treatment efficacy [14]. Studies have indicated good efficacy of HAIC combined with TKIs and ICIs in patients with advanced hepatocellular carcinoma (HCC) [15–17]. According to a previous study, advanced ICC patients treated with lenvatinib plus a programmed cell death-1 (PD-1) inhibitor combined with HAIC had an objective response rate (ORR) of 48.7%, a disease control rate (DCR) of 82.1%, and a 1-year progression-free survival (PFS) rate of 61.9% [18]. Given this evidence, lenvatinib plus ICI combined with HAIC of Gemox (Gemox-HAIC) may be a promising therapy for BTC management, but more studies are needed for validation.

Hence, this study aimed to evaluate the preliminary treatment efficacy and safety profile of lenvatinib plus ICI combined with Gemox-HAIC in BTC patients.

Materials and methods

BTC patients

This retrospective study selected 22 BTC patients who received lenvatinib and ICI combined with Gemox-HAIC treatment between July 2021 and October 2023 from the Electronic Medical Record of our hospital. The inclusion criteria for BTC patients were as follows: (a) diagnosed with BTC by pathohistological and/or cytological examinations [19]; (b) aged ≥ 18 years and either sex; (c) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2; (d) had at least one available imaging assessment data; and (e) were not willing or could not tolerate systemic therapy.

The exclusion criteria for BTC patients were: (a) had autoimmune diseases; (b) had other primary solid tumors or hematological diseases; (c) had no available clinical or follow-up data; and (d) had immunotherapy-related contraindications.

This study obtained approval from the Ethics Committee. All BTC patients or their families signed informed consent forms.

Treatment information

BTC patients received lenvatinib plus ICI combined with Gemox-HAIC treatment, and treatment information was obtained from the electronic medicine system. For the HAIC procedure, a catheter/microcatheter was placed into the main feeding artery of the tumors based on the arteriography results, and then Gemox was administered through the artery as follows: 1000 mg/m^2 of gemcitabine and 85 mg/m^2 of oxaliplatin; the doses were reduced to 75% for patients with a history of intolerance to chemotherapy. The ICI treatment protocol for patients was developed based on the doctor's recommendations, the patient's actual condition, and the patient's preference, which included PD-1 inhibitors and programmed cell death-ligand 1 (PD-L1) inhibitors. Lenvatinib was given orally at a daily dose of 12 mg (for patients with a body weight ≥ 60 kg) or 8 mg (for patients with a body weight < 60 kg). Typically, Gemox-HAIC treatment was stopped after six cycles, followed by treatment with lenvatinib plus ICI until disease progression occurred. The protocol is shown in Supplementary Fig. 1.

Data retrieval and assessment

Data on routine blood parameters, T lymphocyte counts, liver function tests, and tumor-related imaging data were retrieved from the electronic medical system. The computed tomography (CT) or magnetic resonance (MR) evaluations were performed every three months for the first two years and every six months after two years. Patients' best response was assessed via CT or MR according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) standard [20]. A complete response (CR) was defined as no residual malignancy, a partial response (PR) was defined as a decrease of at least 30% in the sum of the diameters of the viable target lesions compared with the baseline sum of the diameters of the target lesions, a stable disease (SD) was defined as neither a response > 30% nor tumor progression > 20%,

and progressive disease (PD) was defined as an increase of at least 20% in the sum of the diameters of the viable target lesions compared with the baseline diameter. Moreover, the ORR and DCR of the BTC patients were calculated. Patients were followed every 1.5 months. The follow-up range was 1.0–28.0 months, and the median was 7.0 months. Eight patients died during the follow-up period. PFS was calculated as the time from the start of treatment to the date of PD or death, and OS was calculated as the duration between the beginning of treatment and the time of death from any cause. Adverse events in BTC patients were also recorded and classified according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Statistical analyses

The data were analyzed via IBM SPSS 23.0 (USA). The missing data were dealt with as follows: the survival data of those patients who lost follow-up were handled as censored data; meanwhile, the baseline missing continuous variables were not specially treated. Chi-square tests and Fisher's exact tests were used for the comparative analysis. Kaplan–Meier curves were used to demonstrate the relationships of patient PFS and OS with baseline characteristics, which were analyzed by the log-rank test. Statistical significance was defined as a P value less than 0.05.

Results

Clinical features

The mean age of the patients was 65.1 ± 8.5 years. There were 12 (54.5%) male patients. Concerning the tumor-node-metastasis (TNM) stage, 2 (9.1%) patients were stage IIIA, 12 (54.5%) patients were stage IIIB, and 8 (36.4%) patients were stage IV. Sixteen (72.7%) patients received the regimen as a first-line treatment, and 6 (27.3%) patients received the regimen as a second-line treatment. With respect to ICI utilization, 3 (13.6%) patients received PD-1 inhibitors, and 19 (86.4%) patients were administered PD-L1 inhibitors. The baseline features are listed in Table 1.

Table 1 Baseline characteristics in all BTC patients

Items	BTC patients (*N* = 22)
Demographic characteristics	
Age (years), mean ± SD	65.1 ± 8.5
Male, No. (%)	12 (54.5)
Smoke history, No. (%)	3 (13.6)
Medical history	
Hypertension history, No. (%)	10 (45.5)
Diabetes history, No. (%)	2 (9.1)
Surgery history, No. (%)	9 (40.9)
Disease characteristics	
ECOG PS, No. (%)	
0	2 (9.1)
1	16 (72.7)
2	4 (18.2)
Primary tumor type, No. (%)	
ICC	14 (63.6)
ECC	1 (4.5)
GBC	7 (31.8)
TNM stage, No. (%)	
IIIA	2 (9.1)
IIIB	12 (54.5)
IV	8 (36.4)
Treatment	
Treatment line, No. (%)	
1st	16 (72.7)
2nd	6 (27.3)
ICI type, No. (%)	
PD-1 inhibitor	3 (13.6)
PD-L1 inhibitor	19 (86.4)
Routine blood parameters	
WBC (10^9/L), mean ± SD	6.4 ± 1.6
Hb (g/L), mean ± SD	122.1 ± 20.9
PC (10^9/L), mean ± SD	222.5 ± 70.2
NEUT (10^9/L), mean ± SD	66.7 ± 8.9
NEUT (%), mean ± SD	4.7 ± 1.4
LYM (10^9/L), mean ± SD	21.7 ± 7.6
LYM (%), mean ± SD	1.3 ± 0.3
T-lymphocyte	
$CD3^+$ T cells (%), mean ± SD	68.2 ± 10.1
$CD4^+$ T cells (%), mean ± SD	42.4 ± 12.2
$CD8^+$ T cells (%), mean ± SD	23.6 ± 7.2
Liver function tests	
AST (U/L), mean ± SD	64.3 ± 47.2
ALT (U/L), median (IQR)	27.5 (20.3–83.8)
T-BIL (μmol/L), median (IQR)	17.1 (11.5–71.1)
D-BIL (μmol/L), median (IQR)	8.2 (5.7–62.2)
I-BIL (μmol/L), median (IQR)	7.4 (6.0-11.4)

Treatment response

The CR rate was 0.0%, the PR rate was 72.7%, the SD rate was 18.2%, and the PD rate was 9.1% (Fig. 1A). The ORR, calculated as the sum of the CR and PR rates, was 72.7% (Fig. 1B). The DCR, calculated as the sum of the CR, PR, and SD rates, was 90.9% (Fig. 1C).

Demographic characteristics, medical history, disease characteristics, and treatment information were not associated with the ORR or DCR (all $P > 0.05$) (Table 2).

PFS and OS

The median (95% confidence interval (CI)) PFS was 6.1 (4.3–8.0) months, and the 12-month accumulating PFS

Table 1 (continued)

Items	BTC patients (*N* = 22)
ALB (g/L), mean ± SD	38.3 ± 5.6
TP (g/L), mean ± SD	67.6 ± 6.6

BTC, biliary tract carcinoma; SD, standard deviation; ECOG, eastern cooperative oncology group; PS, performance status; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; TNM, tumor-node-metastasis; ICI, immune checkpoint inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; WBC, white blood cell; Hb, hemoglobin; PC, platelet count; NEUT, neutralization; LYM, lymphocyte counts; IQR, interquartile range; $CD3^+$, cluster of differentiation 3-positive; $CD4^+$, cluster of differentiation 4-positive; $CD8^+$, cluster of differentiation 8-positive; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-BIL, total bilirubin; D-BIL, direct bilirubin; I-BIL, indirect bilirubin; ALB, albumin; TP, total protein

rate was 26.0% (Fig. 2A). The median (95% CI) OS was 10.3 (8.1–12.5) months, and the 12-month accumulating OS rate was 43.2% (Fig. 2B).

Correlation of baseline features with PFS and OS

Age, sex, smoking history, hypertension history, diabetes history, surgery history, ECOG PS, primary tumor type, TNM stage, treatment line, and ICI type were not associated with PFS (all $P > 0.05$) (Supplementary Fig. 2A-K) or OS (all $P > 0.05$) (Supplementary Fig. 3A-K).

Adverse events

Adverse events included leukopenia (22.7%), thrombocytopenia (22.7%), vomiting (9.1%), nausea (4.5%), fatigue (4.5%), dermatitis (4.5%), and pneumonitis (4.5%). Most of these adverse events were grade 1–2. Only 1 (4.5%) patient had grade 3–4 leukopenia, and 1 (4.5%) patient had grade 3–4 thrombocytopenia (Table 3).

Discussion

BTC is a lethal malignancy with a high mortality rate, and more treatment modalities are being explored to improve patient outcomes [21, 22]. HAIC is a locoregional antitumor treatment, and its combination with lenvatinib plus ICI treatment may have synergistic effects [23]. On the one hand, chemotherapy via HAIC could enhance the function of cytotoxic T cells and dendritic cells to restore immune surveillance, thereby increasing the tumor response to ICI treatment and reducing drug resistance [24, 25]. On the other hand, lenvatinib inhibits tumor angiogenesis and reduces immunosuppression in the tumor microenvironment, which may subsequently increase the delivery of chemotherapy drugs and increase the effectiveness of ICI drugs [26–28]. Thus, the combination of lenvatinib, ICI, and HAIC has achieved a specific response in BTC patients, with an ORR ranging from 39.1 to 48.7% and a DCR ranging from 82.1 to 91.3% [18, 29, 30]. In this study, the ORR was 72.7% in BTC patients who received lenvatinib plus ICI combined with Gemox-HAIC treatment, whereas the DCR was 90.9% in these patients, which was within the range of the rates reported in previous studies [18, 29, 30]. These results showed that the combination of lenvatinib, ICI treatment, and Gemox-HAIC might achieve a promising treatment response in BTC patients. However, more studies are needed for validation. Moreover, previous studies revealed that BTC patients who received lenvatinib plus ICI combined with HAIC treatment exhibited a median PFS of 6.0–11.9 months and a median OS of 11.6–17.9 months [29–32]. This study revealed that the median (95% CI) PFS was 6.1 (4.3–8.0) months and that the OS was 10.3 (8.1–12.5) months in BTC patients who received lenvatinib plus ICI combined with Gemox-HAIC treatment, which was within the range reported in previous studies [29–32]. However, this study did not verify the mechanism of the potential synergistic effects among lenvatinib, ICI, and Gemox-HAIC treatment and requires further investigation.

Some highlights should be discussed in this study. Previous studies have focused on the use of lenvatinib plus ICI combined with HAIC as a first-line treatment for BTC patients [29–32], but the efficacy of this regimen as a second-line treatment in BTC patients lacks clinical evidence. This study used lenvatinib plus ICI combined with Gemox-HAIC as a first- or second-line treatment for BTC patients, showing promising efficacy. This study also showed that the treatment line was not associated with the ORR, DCR, DFS, or OS in BTC patients. These findings suggest that lenvatinib plus ICI combined with Gemox-HAIC as a second-line treatment regimen might also achieve acceptable efficacy in BTC patients. In addition, PD-1 inhibitors are commonly used in studies involving ICI treatment combined with lenvatinib and HAIC [18, 29, 31, 32], whereas investigations of PD-L1 inhibitors utilized in combination regimens are rare. This study included both PD-1 and PD-L1 inhibitors and revealed their encouraging treatment efficacy in combination with lenvatinib and HAIC in BTC patients. The evidence indicated that both PD-1 inhibitors and PD-L1 inhibitors could be effective when combined with lenvatinib and HAIC in BTC patients. Furthermore, FOLFOX-HAIC has been frequently administered with lenvatinib and ICI treatment [29–32], whereas evidence for Gemox-HAIC in combination regimens is lacking. In the present study, Gemox-HAIC treatment revealed encouraging treatment efficacy in combination with lenvatinib and ICI treatment in BTC patients. These results support the potential of Gemox-HAIC as a viable option in combination with lenvatinib and ICI treatment in BTC patients.

Despite the promising treatment benefit of lenvatinib plus ICI combined with HAIC, the incidence of adverse events should also be considered [30, 33, 34]. Thrombocytopenia and leukopenia are common adverse events in patients receiving lenvatinib plus ICI combined with HAIC treatment, which occur in 10.0-39.3% and 32.1-35.3% of these patients, respectively [30, 31, 33, 34]. In

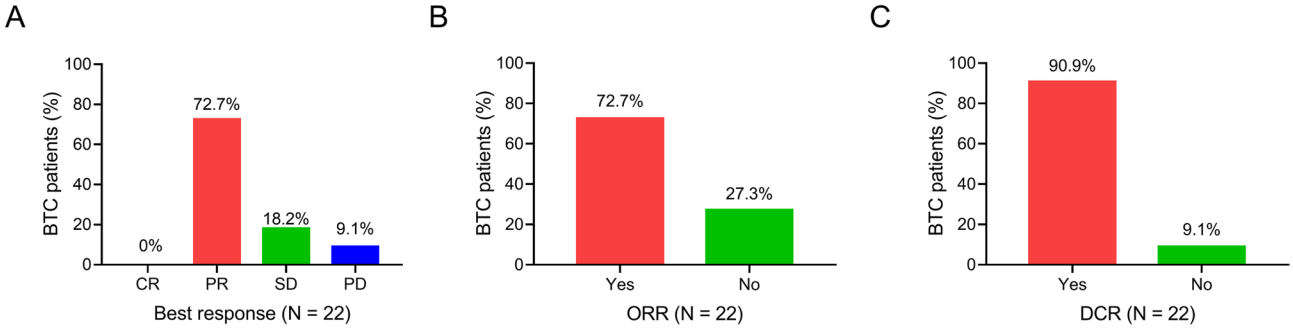
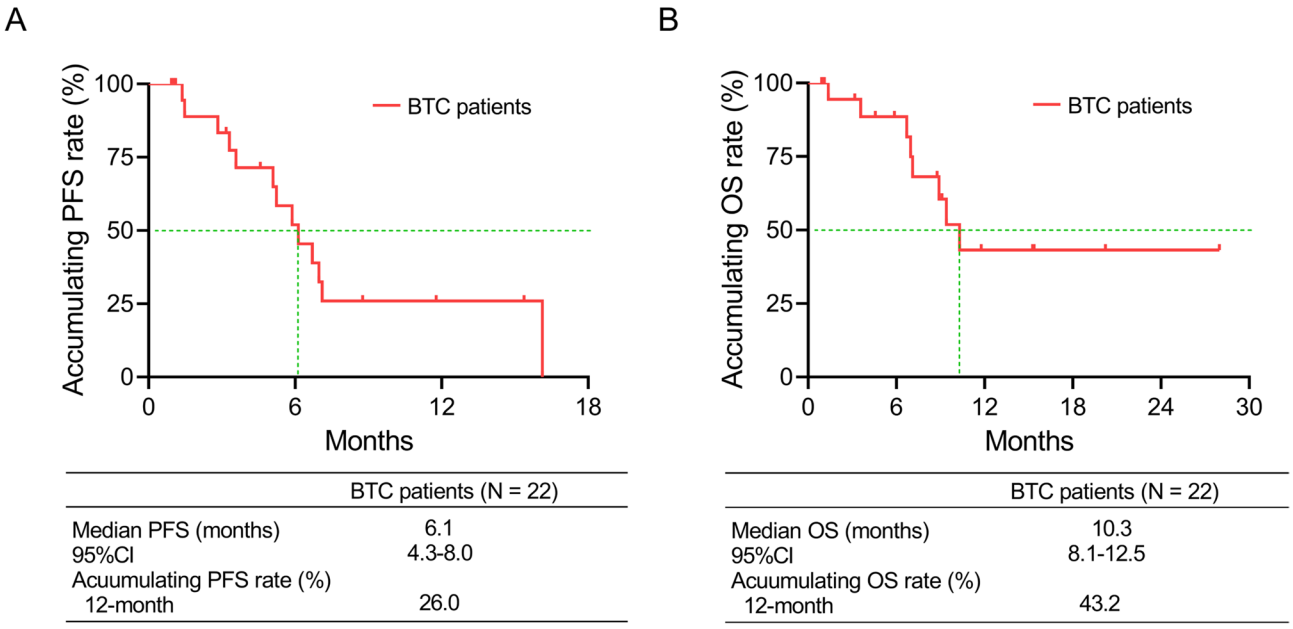


Fig. 1 Treatment response in BTC patients receiving lenvatinib plus ICI combined with Gemox-HAIC treatment. The best response (**A**), ORR (**B**), and DCR (**C**) of BTC patients receiving lenvatinib plus ICI combined with Gemox-HAIC treatment

Table 2 Comparison of baseline characteristics between BTC patients with and without ORR and DCR

Items	ORR		*P* value	DCR		*P* value
	No	Yes		No	Yes	
Age, No. (%)			1.000			0.195
<65 years	3 (30.0)	7 (70.0)		2 (20.0)	8 (80.0)	
≥65 years	3 (25.0)	9 (75.0)		0 (0.0)	12 (100.0)	
Sex, No. (%)			0.348			0.195
Female	4 (40.0)	6 (60.0)		2 (20.0)	8 (80.0)	
Male	2 (16.7)	10 (83.3)		0 (0.0)	12 (100.0)	
Smoke history, No. (%)			1.000			1.000
No	5 (26.3)	14 (73.7)		2 (10.5)	17 (89.5)	
Yes	1 (33.3)	2 (66.7)		0 (0.0)	3 (100.0)	
Hypertension history, No. (%)			0.646			
No	4 (33.3)	8 (66.7)		2 (16.7)	10 (83.3)	0.481
Yes	2 (20.0)	8 (80.0)		0 (0.0)	10 (100.0)	
Diabetes history, No. (%)			1.000			1.000
No	6 (30.0)	14 (70.0)		2 (10.0)	18 (90.0)	
Yes	0 (0.0)	2 (100.0)		0 (0.0)	2 (100.0)	
Surgery history, No. (%)			0.178			1.000
No	2 (15.4)	11 (84.6)		1 (7.7)	12 (92.3)	
Yes	4 (44.4)	5 (55.6)		1 (11.1)	8 (88.9)	
ECOG PS, No. (%)			0.110			
0	0 (0.0)	2 (100.0)		0 (0.0)	2 (100.0)	0.481
1	3 (18.8)	13 (81.3)		1 (6.3)	15 (93.8)	
2	3 (75.0)	1 (25.0)		1 (25.0)	3 (75.0)	
Primary tumor type, No. (%)			0.530			0.182
ICC	3 (21.4)	11 (78.6)		0 (0.0)	14 (100.0)	
ECC	0 (0.0)	1 (100.0)		0 (0.0)	1 (100.0)	
GBC	3 (42.9)	4 (57.1)		2 (28.6)	5 (71.4)	
TNM stage, No. (%)			0.378			1.000
IIIA	1 (50.0)	1 (50.0)		0 (0.0)	2 (100.0)	
IIIB	2 (16.7)	10 (83.3)		1 (8.3)	11 (91.7)	
IV	3 (37.5)	5 (62.5)		1 (12.5)	7 (87.5)	
Treatment line, No. (%)			0.634			0.481
1st	5 (31.3)	11 (68.8)		1 (6.3)	15 (93.8)	
2nd	1 (16.7)	5 (83.3)		1 (16.7)	5 (83.3)	
ICI type, No. (%)			0.532			1.000
PD-1 inhibitor	0 (0.0)	3 (100.0)		0 (0.0)	3 (100.0)	
PD-L1 inhibitor	6 (31.6)	13 (68.4)		2 (10.5)	17 (89.5)	

ORR, objective response rate; DCR, disease control rate; BTC, biliary tract carcinoma; ECOG, eastern cooperative oncology group; PS, performance status; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; TNM, tumor-node-metastasis; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1



	BTC patients (N = 22)
Median PFS (months)	6.1
95%CI	4.3-8.0
Acuumulating PFS rate (%)	
12-month	26.0

	BTC patients (N = 22)
Median OS (months)	10.3
95%CI	8.1-12.5
Acuumulating OS rate (%)	
12-month	43.2

Fig. 2 K–M curves of PFS and OS in BTC patients receiving lenvatinib plus ICI combined with Gemox-HAIC treatment. PFS (**A**) and OS (**B**) of BTC patients receiving lenvatinib plus ICI combined with Gemox-HAIC treatment

Table 3 Cox regression analysis for PFS

Items	Univariate analysis		Multivariate analysis	
	P value	HR (95%CI)	*P* value	HR (95%CI)
Age (≥ 65 years vs. <65 years)	0.627	1.332 (0.420–4.223)	0.051	1351.615 (0.978-1867332.290)
Sex (male vs. female)	0.873	0.911 (0.291–2.857)	0.221	0.112 (0.003–3.743)
Smoke history (yes vs. no)	0.915	0.920 (0.198–4.277)	0.369	0.178 (0.004–7.678)
Hypertension history	0.733	0.820 (0.262–2.568)	0.031	0.000 (0.000-0.410)
Diabetes history	0.533	0.521 (0.067–4.052)	0.605	0.427 (0.017–10.749)
Surgery history	0.560	1.411 (0.443–4.496)	0.340	3.651 (0.255–52.308)
ECOG PS (per score)	0.169	2.786 (0.647–11.993)	0.100	24.144 (0.544-1072.296)
Primary tumor type (ECC or GBC vs. ICC)	0.800	1.188 (0.313–4.508)	0.085	0.033 (0.001–1.611)
TNM stage (per stage)	0.628	1.261 (0.494–3.215)	0.080	0.014 (0.000-1.658)
Treatment line (2nd vs. 1st)	0.253	1.990 (0.612–6.475)	0.029	463.928 (1.894-113617.134)
ICI type (PD-L1 inhibitor vs. PD-1 inhibitor)	0.757	1.272 (0.277–5.836)	0.353	0.126 (0.002–10.044)

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, eastern cooperative oncology group; PS, performance status; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; TNM, tumor-node-metastasis; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1

addition, grade 3–4 thrombocytopenia and leukopenia are observed in 0.0-10.7% and 0.0-5.9% of these patients, respectively [30, 31, 34]. In this study, the most common adverse events included thrombocytopenia and leukopenia, with incidences of both 22.7% in BTC patients who received lenvatinib plus ICI combined with Gemox-HAIC treatment. The incidence rates of grade 3–4 thrombocytopenia and leukopenia were 4.5%, which are in the range of previously reported data [30, 31, 33, 34]. Moreover, most of the adverse events were grades 1–2 in BTC patients who received lenvatinib plus ICI combined with HAIC treatment. Therefore, the adverse effects of lenvatinib plus ICI combined with Gemox-HAIC treatment were acceptable in BTC patients.

Limitations still exist in the present study. First, this was a retrospective study, leading to unavoidable confounding factors. Second, owing to the low incidence of BTC [1] and the small number of patients who are willing to undergo HAIC, the sample size was relatively small in this study, which resulted in weakened statistical power and statistical insignificance in most of the results. Consequently, future investigations with larger sample sizes are warranted for validation. Finally, this was a single-arm study. However, the superiority of lenvatinib plus ICI combined with Gemox-HAIC treatment over other regimens in BTC patients is uncertain and requires further investigation.

Conclusions

In summary, lenvatinib plus ICI combined with Gemox-HAIC treatment shows preliminary efficacy and acceptable safety profiles in BTC patients. These findings indicate that lenvatinib plus ICI combined with Gemox-HAIC treatment is a potential choice for BTC patients, but validation in studies with larger sample sizes is warranted.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-025-03882-3.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

Author contributions
Junying Wang: Conceptualization, Formal analysis, Methodology, Project administration, Writing - original draft, Writing - review & editing. Guangyu Zhu: Data curation, Investigation, Methodology, Resources, Writing - original draft, Writing - review & editing. Jinhe Guo: Data curation, Investigation, Methodology, Resources, Writing - original draft, Writing - review & editing. Gaojun Teng: Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study obtained approval from the Ethics Committee. All BTC patients or their families signed informed consent forms.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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