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RESEARCH

Analysis of the effectiveness and safety of lenvatinib/bevacizumab combined with PD-1/PD-L1 inhibitors and GEMOX in the first-line treatment of advanced biliary tract carcinoma

Lu Zhao[1] · Zhengfeng Zhang[1] · Dazhen Wang[1] · Liu Yang[1] · Ze Liu[1] · Changjie Lou[1]

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Abstract

To assess the efficacy and safety of lenvatinib/bevacizumab combined with programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors and gemcitabine/oxaliplatin (GEMOX) as first-line treatments in patients with advanced biliary tract cancer (BTC). Patients with advanced BTC who received lenvatinib/bevacizumab combined with PD-1/PD-L1 inhibitors plus gemcitabine/oxaliplatin (GEMOX) chemotherapy were retrospectively screened. The primary endpoints were overall survival (OS) and progression-free survival (PFS), whereas the secondary endpoints were objective response rate (ORR), disease control rate (DCR), and safety. Prognostic factors for survival were analyzed. A total of 172 individuals were enrolled and categorized into four groups: Group A received GEMOX plus PD-1 antibody (sintilimab or camrelizumab) and lenvatinib; group B received GEMOX and PD-1 antibody (sintilimab or camrelizumab) and bevacizumab; group C received GEMOX and PD-1 antibody (sintilimab or camrelizumab); and group D received GEMOX alone. The median OS was 13.63 months (95% confidence interval [CI]: 12.37–14.89), 12.41 months (95% CI: 10.67–12.32), 11.23 months (95% CI: 9.39–13.07), and 8.86 months (95% CI: 7.28–10.44) in groups A, B, C, and D, respectively ($P = 0.312$). In groups A, B, C, and D, the median PFS was 12.42 months, 11.05 months, 8.89 months, and 6.02 months. A statistically significant difference was observed (t = 2, 95% CI: 11.31–13.53, $P < 0.01$). The ORR was 45.00% (17/40) in group A, 34.78% (16/46) in group B, 16.67% (5/30) in group C, and 17.86% (10/56) in group D. The DCR was 87.50% (35/40), 78.26% (36/46), 76.67% (23/30), and 58.93% (33/56) in groups A, B, C, and D, respectively. In addition, regression analysis showed that patients' metastasis site, whether the neutrophil–lymphocyte ratio was < 2.3, and whether chemotherapy was administered through hepatic artery embolization and was independent prognostic factors influencing median OS and PFS. Almost all patients included in the study experienced treatment-related adverse events (TRAEs) of varying degrees of severity, with grade 1–2 adverse events predominating. Lenvatinib/bevacizumab combined with programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors and gemcitabine/oxaliplatin (GEMOX) represent an effective and tolerable regimen for advanced BTC in a multicenter retrospective real-world study.

Keywords Biliary tract cancer · Lenvatinib · Bevacizumab · Immunotherapy · Efficacy · Safety

Introduction

Biliary tract carcinoma (BTC) is a spectrum of malignance primarily arising from the epithelial cells of the biliary duct and gallbladder. It can be divided into the cholangiocarcinoma (CCA), gallbladder carcinoma (GBC), and ampullary cancer (AMPAC) subtypes, each of which is a rare cancer with an incidence <6 per 100,000 [1].

According to the anatomic location, CCA is classified into intrahepatic and extrahepatic CCA and accounts for approximately 2% of the annual cancer-related deaths worldwide [2]. The incidence of intrahepatic CCA is on the rise, but the mortality rate of extrahepatic CCA and GBC is decreasing, and each subtype is distinct in respect to epidemiology, clinical behavior, and therapeutic characteristics [3]. The pathogenesis of BTC is so unclear that the prognosis of BTC is quite poor due to the diagnosis occurring at a

✉ Changjie Lou
601245@hrbmu.edu.cn

[1] Department of Gastroenterology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province, China

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late stage of disease in the majority of patients, resulting in a year survival rate of only 2%.

Currently, gemcitabine- or fluorouracil-based systemic chemotherapy remains the mainstay of the first-line treatment for advanced BTC. The regimen of gemcitabine and oxaliplatin (GEMCIS) confers a median overall survival (OS) of 11.7 months and a progression-free survival (PFS) of 8.0 months [4]. On account of its better tolerability, oxaliplatin is extensively used in the treatment of BTC but has not been examined in a large-scale, prospective controlled study. Fiteni *et al.* analyzed the efficacy of GEMCIS and gemcitabine and oxaliplatin (GEMOX) by reviewing a total of 33 studies of 1,470 patients, which demonstrated that although GEMOX prolongs the median OS (9.7 *vs.* 9.5 months) and median PFS (6.3 *vs.* 4.9 months), it also increases the incidence of grade 3toxicities [5] . Thus, there is a pressing need to develop a new effective strategy to extend the benefit in first-line treatment of BTC, which is pivotal to improving the OS of these patients.

With the emergence of ICI therapy, novel inhibitors of programmed death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) have been investigated in relation to BTC by way of combination with targeted agents and/or chemotherapy. In the KEYNOTE-158 trials, monotherapy with pembrolizumab, an inhibitor of programmed cell death protein 1 (PD-1), was reported to yield an objective response in 5.8% of all patients who underwent second-line treatment of BTC; however, this objective response only occurred in 13.0% of PD-L1-positive patients in the KEYNOTE-028 study [6]. Furthermore, immunochemotherapy was demonstrated to be effective in another PD-1 inhibitor, camrelizumab, in combination with the FOLFOX4/GEMOX regimen, deriving an objective response rate (ORR) of 16.3% and a disease control rate (DCR) of 75.0% in first-line treatment in a phase II trial [7]. However, combination therapy brings better survival benefits; it also entails greater toxicity. Thus, there is an urgent need for the effective treatment of BTC with better tolerance.

Targeted therapy has emerged as a prominent area of investigation within oncology research over the past several years. Lenvatinib is a multi-targeted inhibitor that suppresses vascular endothelial growth factor receptor (VEGFR) 1–3, fibroblast growth factor receptor (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR)α, and proto-oncogenes RET and KIT [8]. Preclinical data show that lenvatinib decreases the number of tumor-associated macrophages, thereby affecting antitumor immune responses and leading to increased efficacy of PD-L1 inhibition [9]. In a recent study, Dr. Zhao tested the efficacy and safety of pembrolizumab plus lenvatinib as a second-line treatment for advanced biliary tract cancer [10]. The trial showed an objective response rate (ORR) of 25% and a disease control rate (DCR) of 78.1%. Notably, no grade 5 adverse events were reported and only 59.3% of patients suffered from grade 3 treatment-related adverse events.

Bevacizumab is a vascular endothelial growth factor A-specific angiogenesis inhibitor. By neutralizing VEGF, bevacizumab prevents the activation of VEGF tyrosine kinase receptors VEGFR1 and VEGFR2 on endothelial cells [11]. The addition of bevacizumab (a VEGF monoclonal antibody) to gemcitabine/oxaliplatin demonstrated good tolerability and antitumor activity in advanced BTC in a single-arm phase II trial. Besides, IMbrave 151, a randomized, double-blind, placebo-controlled multicenter phase II study, designed to evaluate the efficacy and safety of atezolizumab with bevacizumab in combination with Cis/Gem, compared with atezolizumab plus Cis/Gem, showed that atezolizumab combined with bevacizumab and platinum-based chemotherapy significantly improved PFS, OS, and ORR in patients with advanced BTC (iCCA, eCCA, and GBC) [12].

Based on preclinical data, we conducted a retrospective study to evaluate the safety and efficacy of lenvatinib bevacizumab combined with PD-1/PD-L1 (sintilimab or camrelizumab) inhibitors (sintilimab or camrelizumab) and GEMOX in the first-line treatment of advanced biliary tract carcinoma.

Materials and methods

Patients

This study was reviewed and approved by the Board of Directors of Harbin Medical University Cancer Hospital for inclusion in the review. Study participants provided written informed consent for the publication of any potentially identifiable image or data contained herein. The retrospective study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital prior to being performed (approval number is: KY2022-14), which follows the World Medical Association Declaration of Helsinki (as revised in 2013). Patients were enrolled according to the following eligibility criteria: 18 years or older with physiologically identified advanced BTC; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; Child-Pugh class A–B liver function; received gemcitabine-based chemotherapy as the first-line treatment, which could include regimens of chemotherapy only, in combination with targeted agent, or with immunotherapy of camrelizumab or other PD-1/PD-L1 (sintilimab or camrelizumab) inhibitor; and with at least one measurable intrahepatic lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The exclusive criteria included patients with other malignant tumors; those with severe respiratory, cardiovascular, or kidney disease; those pregnant

or lactating; those with incomplete medical information; and those loss to follow-up.

Baseline clinical information

Name, age, height, gender, history of alcohol and drug use, body weight, primary lesion site, histological grading, ECOG score, time of initial diagnosis, history of radical surgery, postoperative adjuvant chemotherapy, radiotherapy, radiofrequency ablation, hepatic artery perfusion chemotherapy, distant metastasis, and outcomes of laboratory tests prior to and following the procedure should all be noted. Following chemotherapy, regular blood tests, liver function tests, thyroid function tests, tumor markers, imaging test results, genetic test reports, tumor efficacy assessments, progression time and cause, survival status, cause and time of death, adverse events related to treatment, and post-discharge diagnosis and management are routinely monitored (Table 1).

Treatments

Patients were divided into four arms according to the regimens. Arm A included patients who were treated with ICIs (sintilimab or camrelizumab), a targeted agent with Lenvatinib which was administered orally at a dose of 12 mg (for patients with body weight ≥ 60 kg) or 8 mg (for patients with body weight < 60 kg) once a day; arm B included patients treated with ICIs (sintilimab or camrelizumab), a targeted agent with bevacizumab recommended at a dose 15 mg/kg body weight intravenously (IV) every 3 weeks; arm C included patients treated with ICIs (sintilimab or camrelizumab) and GEMOX chemotherapy; and arm D included patients treated with GEMOX regimen chemotherapy only. In arm A, B, and arm C, ICIs (sintilimab or camrelizumab) included camrelizumab (200 mg q2w, IV) or Sindeli (100 mg q3w, IV). The GEMOX regimen consisted of 1 g/m^2 of gemcitabine on day 1 and day 8 with 85 mg/m^2 of oxaliplatin on day 1 (q3w). Patients were treated until disease progression or intolerable toxicities.

Patients were followed up weekly, based on the drug administration cycle.

Evaluation of the efficacy of treatment

The clinical objective response was measured using the RECIST v1.1 criteria and evaluated by professional radiologists at the PUMCH. To assess tumor growth rate and treatment response, computed tomography (CT)/magnetic resonance imaging or positron emission tomography CT images were regularly evaluated. PFS, OS, ORR, DCR, and clinical benefit rate (CBR) were used to assess treatment efficacy. CBR was defined as the proportion of patients with a radiologically confirmed objective response (CR or PR) or SD for > 6 months. Safety assessments and grading were recorded from the electronic medical records of patients or collected by the investigators using the Common Terminology Criteria for Adverse Events (version 5.0) as a reference. Subgroup analyses were also performed. PD-L1 expression was evaluated by immunohistochemistry of formalin-fixed, paraffin embedded tumor specimens, and PD-L1 overexpression was defined as more than 5% positive expression in tumor cells.

Follow-up data

The follow-up was carried out by re-admission to hospital and telephone contact, with the last follow-up in July 2023. The primary endpoint of this study was OS, defined as the time from the first treatment to death from any cause. Secondary endpoints included PFS, which was defined as the time from the beginning of the lenvatinib or bevacizumab treatment to the first tumor progression or death, ORR, DCR, and adverse events.

Statistical analysis

Statistical analyses were performed using SPSS v27.0 software (IBM, Armonk, NY, USA), and the graph was generated using GraphPad Prism 9.0 software. Measurement data with normal distribution were expressed as mean ± standard deviation, and independent sample *t* test was used for comparison between groups. Count data were described as the number of cases (percentage), and the comparison between groups was performed by Chi-square test or Fisher's exact test. Survival outcomes were calculated using the Kaplan–Meier method, and the survival rate was compared with a Logrank test. Influential factors were analyzed using the COX hazard regression model, and all variables with a *p*-value < 0.05 in the univariate analysis were subjected to multivariate analysis. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated. All p-values were two-sided, with p-values < 0.05 considered statistically significant.

Results

The examination of individual clinical data from the combined therapy and chemotherapy groups included data on the first-line treatment for advanced biliary malignancies in 172 patients (Fig. 1 and Table 1). All patients had ECOG scores ranging from 0 to 1. There were no statistically significant differences in age (p=0.054), gender (p=0.874), height (p=0.376), weight (p=0.454), tumor location (p=0.401), and so forth between the four groups. PFS was significantly

Table 1 Baseline characteristics

contents	A (n = 40) N Proportion (%)	B (n = 46) N Proportion (%)	C (n = 30)N Proportion (%)	D (n = 56) N Proportion (%)	*P*-value
Use targeted therapy	Yes	Yes	No	No	< 0.001
Gender					0.874
Male	24(55.81)	21(48.83)	24(55.81)	18(41.86)	
Female	19(44.19)	22(51.16)	19(44.19)	25(58.14)	
Age					0.038
< 60	12(27.91)	15(34.88)	20(46.51)	22(51.16)	
≥ 60	31(72.09)	28(65.12)	23(53.49)	21(48.84)	
ECOG performance, n(%)					0.853
0	10(23.26)	9(20.93)	15(34.88)	8(18.60)	
1	33(76.74)	34(79.07)	28(65.12)	35(81.40)	
PD-L1(CPS Score%)					0.0076
≥ 1%	15(34.88)	14(32.56)	17(39.53)	-	
< 1%	4(9.30)	8(18.60)	7(16.28)	-	
Unknown	24(55.81)	21(48.84)	19(44.19)	-	
Tumor location					0.401
ICC	18(41.86)	15(34.88)	13(30.23)	9(20.93)	
HCCA	2(4.65)	4(9.30)	3(6.98)	2(4.65)	
DCCA	0(0.00)	5(11.63)	8(18.60)	3(6.98)	
GCA	10(23.26)	7(16.28)	4(9.30)	7(16.28)	
Unknown	13(30.23)	12(27.91)	15(34.88)	22(51.16)	
Histologic differentiation					0.215
Wel	16(37.21)	13(30.23)	12(27.91)	9(20.93)	
Moderately	10(23.36)	7(16.28)	14(32.56)	16(37.21)	
Poorly	0(0.00)	1(2.32)	3(6.98)	8(18.60)	
Unknown	17(39.53)	22(51.16)	14(32.56)	10(23.36)	
Number of recurrent organs					0.038
Single	16(37.21)	15(34.88)	14(32.56)	25(58.14)	
Multiple	27(62.79)	28(65.12)	29(67.44)	18(41.86)	
Radical surgery					0.64
Yes	28(65.12)	29(67.44)	27(62.79)	31(72.09)	
No	15(34.88)	14(32.56)	16(37.21)	12(27.91)	
Radiation therapy					0.553
Yes	3(6.98)	5(11.63)	3(6.98)	1(2.33)	
No	40(93.02)	38(88.37)	40(93.02)	42(97.67)	
Evaluation of curative effect					< 0.001
CR	0(0.00)	0(0.00)	0(0.00)	0(0.00)	
PR	16(37.21)	34.88% (15/43)	10(23.26)	1(2.33)	
SD	20(46.51)	41.86% (18/43)	23(53.49)	25(58.14)	
PD	6(13.95)	39.53% (17/43)	10(23.26	17(39.53)	
NLR					0.066
< 2.30	12(27.91)	14(32.56)	15(34.88)	12(27.91)	
≥ 2.30	21(48.84)	29(67.45)	28(65.12)	21(48.84)	
Increase in bilirubin					0.203
Yes	38(88.37)	36(83.72)	14(32.56)	29(67.45)	
No	5(11.63)	7(16.28)	29(67.45)	14(32.56)	
Increase in tumor markers					0.034
Yes	20(46.52)	23(53.49)	14(32.56)	26(60.47)	
No	23(53.49)	20(46.51)	29(67.45)	17(39.54)	
CA199					0.191

Table 1 (continued)

contents	A (n = 40) N Proportion (%)	B (n = 46) N Proportion (%)	C (n = 30)N Proportion (%)	D (n = 56) N Proportion (%)	*P*-value
increase					
Yes	15(34.88)	16(37.21)	23(53.49)	16(37.21)	
No	28(65.12)	27(62.79)	20(46.51)	27(62.79)	

CPS combined positive score, *ECOG* Eastern Cooperative Oncology Group, *GCA* gallbladder carcinoma, *HCCA* hila cholangiocarcinoma, *DCCA* distal cholangiocarcinoma, *ICCA* intrahepatic cholangiocarcinoma, *NLR* neutrophil–lymphocyte ratio, *PD* progressive disease, *PD-L1* programmed cell death ligand 1, *PR* partial response, *SD* stable disease

p-value < 0.05 are indicated in bold

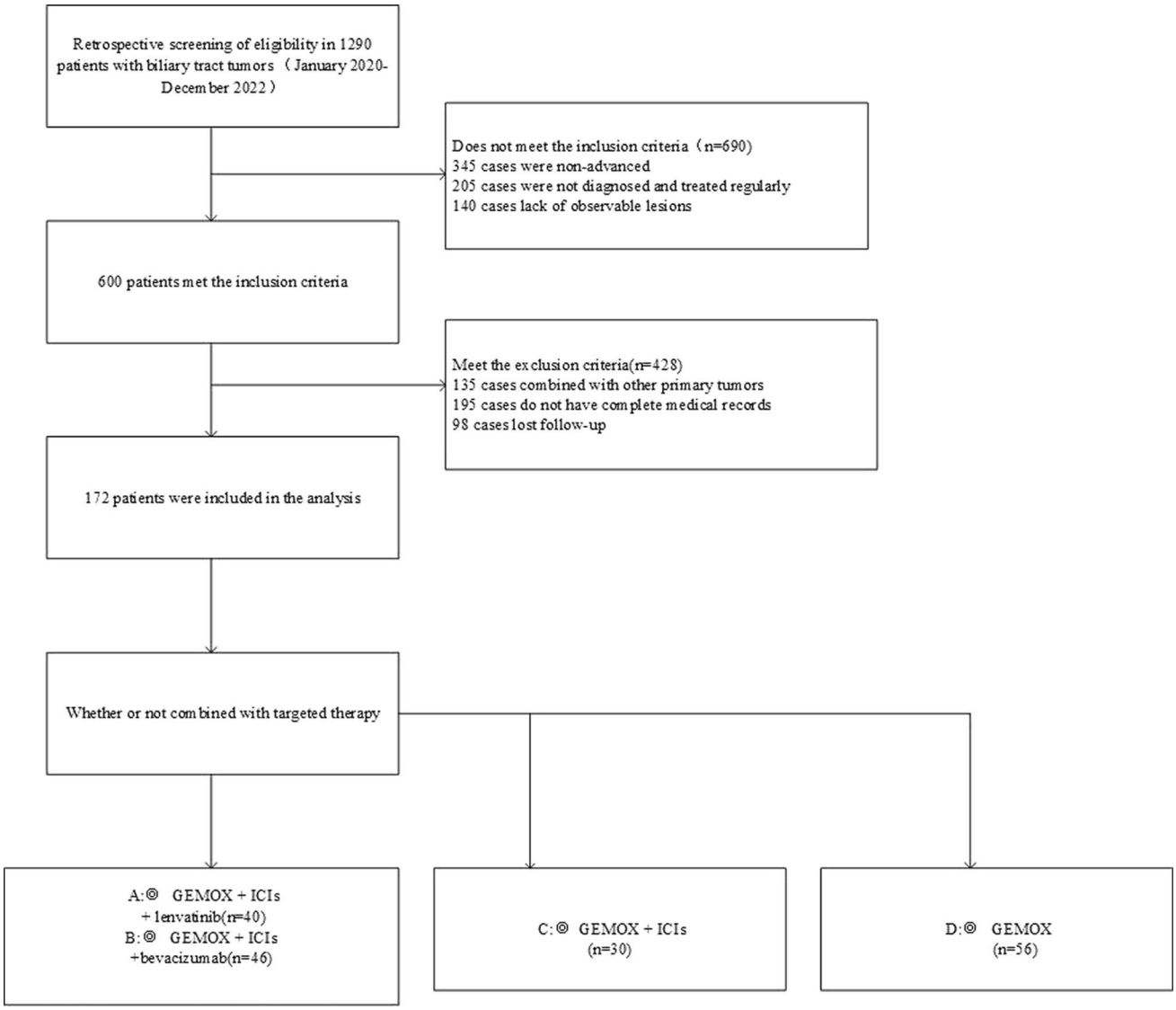


Fig. 1 Flow diagram of study design

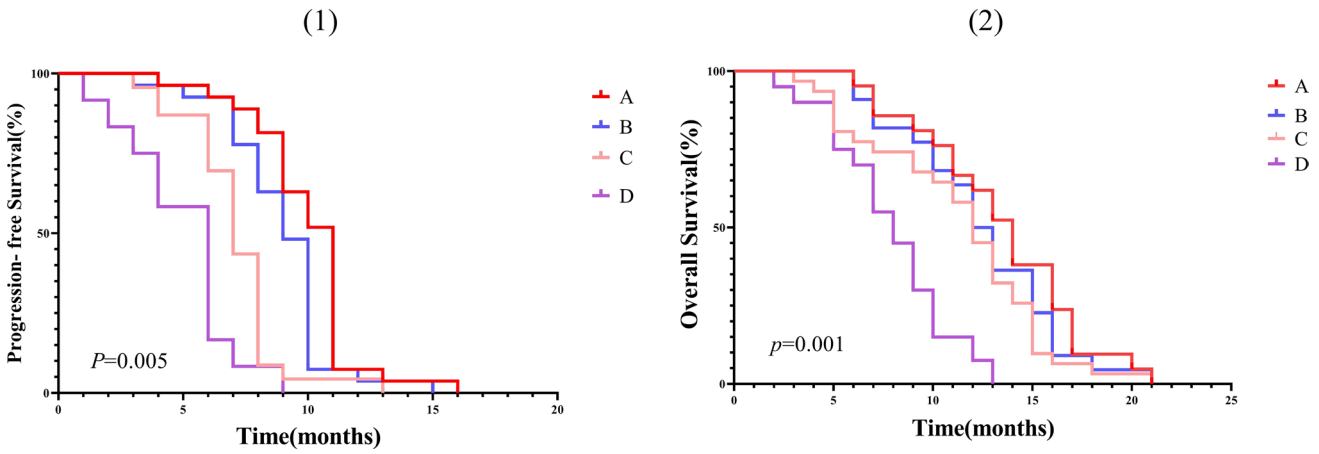


Fig. 2 (1) Kaplan–Meier curve for progression-free survival according to treatment therapy. (2) Kaplan–Meier curve for overall survival according to treatment therapy mPFS, median progression-free survival;mOS, median overall survival; NR, not reached. A: GEMOX + ICIs(sintilimab or camrelizumab) + lenvatinib B:GEMOX + ICIs(sintilimab or camrelizumab) + bevacizumab C:GEMOX + ICIs(sintilimab or camrelizumab)D:GEMOX

lower in group B (11.05 ± 7.00), group C (8.89 ± 8.00), and group D (6.02 ± 6.00) compared to group A (12.42 ± 12.00), with statistical significance ($P < 0.0001$, Fig. 2).

Efficacy analysis

In this study, a minimum of two treatment cycles was administered to 40 patients in group A, followed by an efficacy evaluation. Among these patients, the trial yielded no patients with CR: PR, 45.00% (17/40); CCA, 13.95% (6/40); SD, 45.00% (18/40); CCA, 25.00% (10/40); GCA, 20.00% (8/40); PD, 12.50% (5/40); CCA, 5.00% (2/40); and GCA, 7.50% (3/40). In group A, the DCR was 87.50% (35/40), and the ORR was 45.00% (17/40) (Fig. 3 and Table2).

In group B, 46 patients received at least two evaluations, with a mean treatment duration of 16 ± 2 cycles. No CR was observed; 34.78% (16/46) had PR, including 15 (32.61%) with CCA and 1 (2.17%) with GCA; 43.48% (20/46) had SD, including 15 (32.61%) with CCA and 5 (10.87%) with GCA; and 23.26% (10/43) had PD, including 4 (8.70%) with CCA, 2 (4.35%) with GCA, and 4 (8.70%) were GCA. In the combined therapy group, the overall DCR was 78.26% (36/46) and the overall ORR was 34.78% (16/46).

The mean treatment period in group C was 10 ± 2 cycles, and 30 patients were evaluated at least once. The number of patients who achieved CR in the study was 0%; PR was 16.67% (5/30), including 16.67% (5/30) with CCA; SD was 45.00% (18/30), including 33.33% (10/30) with CCA, and 26.67% (8/30) with GCA; PD was 26.67% (8/30), including 37.21% (6/30) with CCA and 20.00% (2/30) with GCA. The ORR in group C was 16.67% (5/30), and the DCR was 76.67% (23/30).

The mean treatment period in group D was 5 ± 2 cycles, and 56 patients were evaluated at least once. The number of patients who achieved CR in the study was 0; PR was 17.86% (10/56), including 10.71% (6/56) with CCA and 7.14 (4/56) with GCA; SD was 41.07% (23/56), including 23.21% (13/56) with CCA and 17.86% (10/56) with GCA; and PD was 58.93% (33/56), including 46.43% (26/56) with CCA and 12.50% (7/56) with GCA. Group D had an ORR of 17.86% (10/56) and a DCR of 58.93% (33/56).

An instance of survival

Thirteen out of the 172 patients died during the follow-up period, with A median duration of follow-up for the entire population being 10.2 months (95% CI: 9.7–10.7) at the time of the last follow-up (two patients in group A, two patients in group B, four patients in group C, and seven patients in group D). For the entire population, the median PFS was 9.74 months (95% CI: 8.8–10.6) (Fig. 4). With $P < 0.05$, the median PFS in groups A, B, C, and D was 12.4 months, 11.05 months, 8.9 months, and 6.0 months, respectively. The median OS in groups A, B, C, and D was 13.63 months, 12.41 months, 11.24 months, and 8.87 months, respectively, and these results were considered statistically significant ($P = 0.001$ and $P < 0.05$, Fig. 4).

Analysis of factors affecting PFS and OS

Unifactorial and multifactorial analysis of factors affecting PFS

Age, sex, CA19-9 level, the neutrophil-lymphocyte ratio (NLR), and other univariate variables were used as

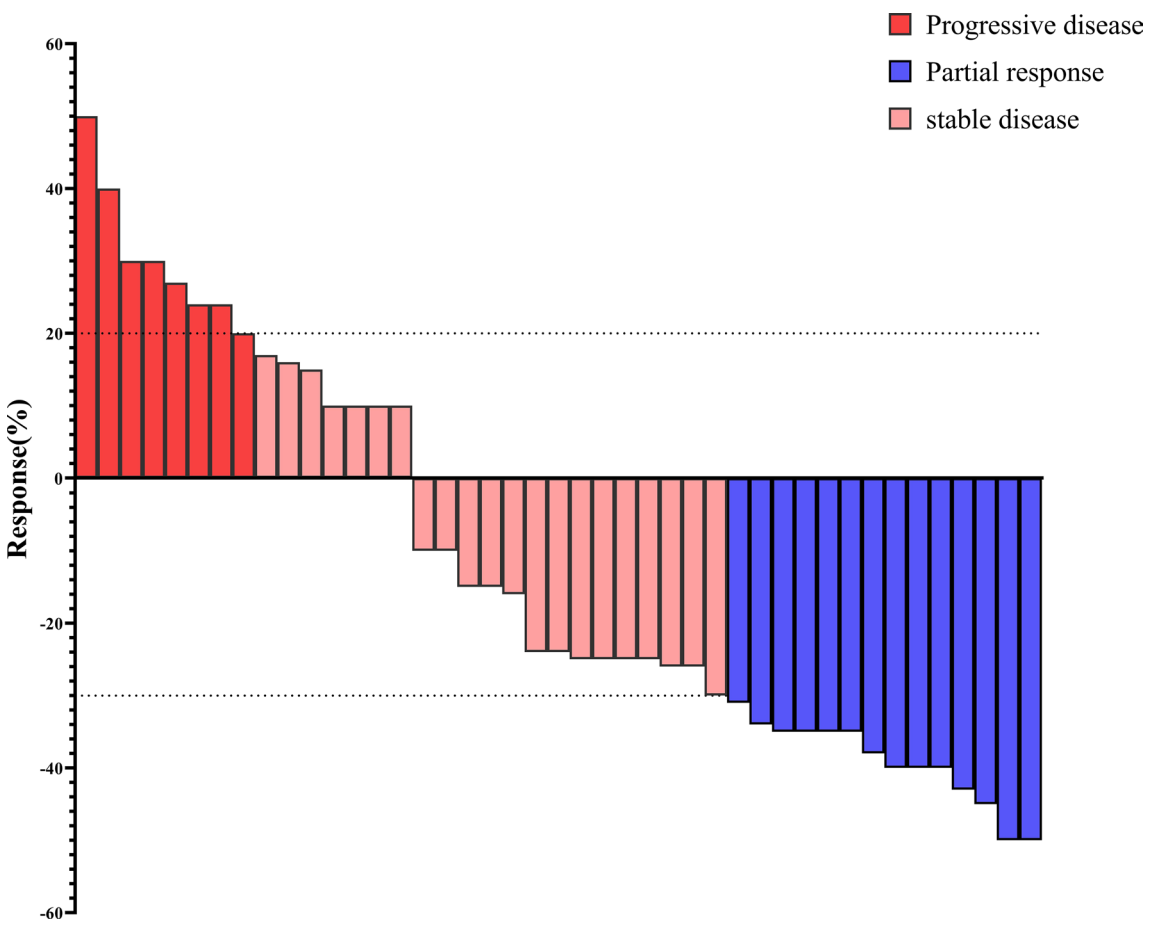


Fig. 3 Maximum percentage reduction of target lesions from baseline in the CI arm ($n = 43$)

Table 2 Summary of best response

	A	B	*P*
CR	0%(0.00)	0%(0.00)	–
PR	45.00% (17/40)	34.78% (16/46)	0.001
SD	45.00% (18/40)	43.48% (20/46)	0.143
PD	12.50% (5/40)	23.26% (10/43)	0.007
ORR	45.00% (17/40)	34.78% (16/46)	0.002
DCR	87.50% (35/40)	78.26% (36/46)	0.006

A: GEMOX + ICIs (sintilimab or camrelizumab) + lenvatinib

B: GEMOX + ICIs(sintilimab or camrelizumab) + bevacizumab

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *DCR* disease control rate

independent variables in a one-way analysis using a Cox regression model. Variables that were significant in the one-way analysis ($P < 0.1$) were included in the multivariate Cox regression analysis. This revealed that the patients' metastasis site (HR = 1,145, 95% CI: 0.28–0.73, $P = 0.001$), whether the NLR ratio was < 2.3 (HR = 0.054, 95% CI: −5.607–2.178, $P < 0.001$) and whether chemotherapy was administered through hepatic artery embolization (HR = 1.237, 95% CI: 1.26–21.11, $P = 0.001$) could impact the patients' PFS (Table 3 and Fig. 5) and have a better prognosis.

Analysis of the factors influencing OS, both single and multi-factor.

The Cox regression model was used for univariate analysis, and the variables of univariate components (age, sex, CA199 level, NLR, etc.) were employed as independent variables, with death as the outcome and OS as the time. The multivariate Cox regression analysis included variables that were significant in the univariate analysis ($P < 0.1$). The findings indicated that the patients' OS may be impacted by the location of their metastatic foci (95% CI: 0.30–0.78, $P = 0.002$) and whether the NLR ratio < 2.3 (95% CI: −5.607−2.178, $P < 0.001$) and whether chemotherapy was administered through hepatic artery embolization (95% CI: 1.13–19.09, $P = 0.043$) could have an positive impact on the OS (Table 4 and Fig. 5).

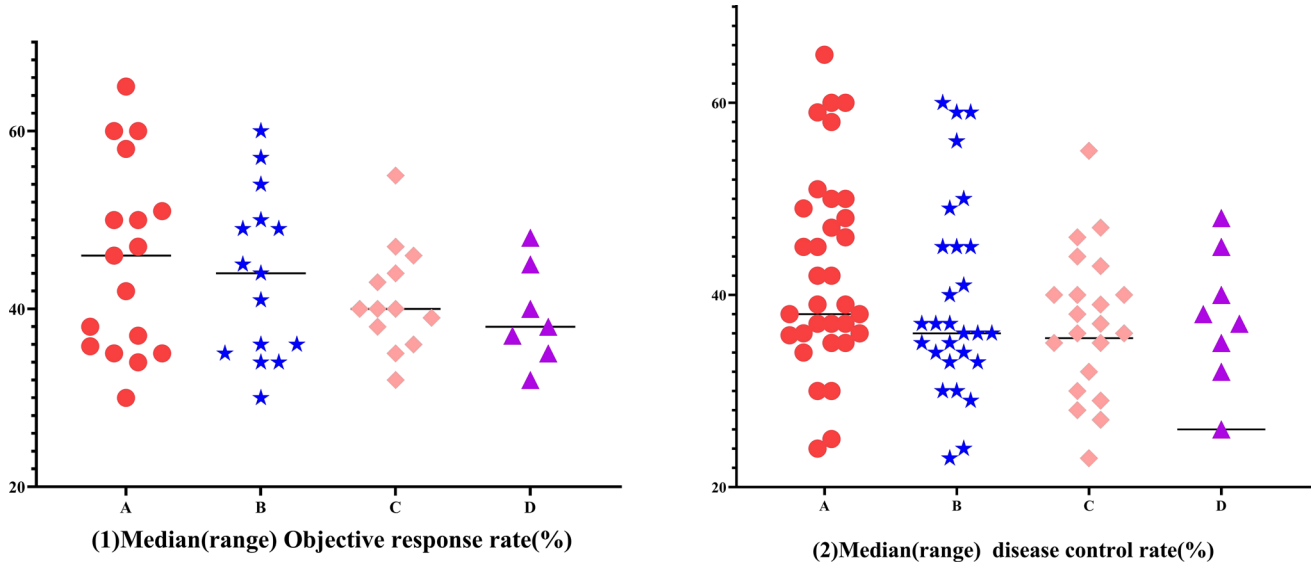


Fig. 4 The ORR and the DCR by the different treatment regimes. (1) ORR by different treatment regimens and (2) DCR by different treatment regimens. Median (range) values across different treatment regimens were calculated from median values reported in individual studies where available. DCR, disease control rate; ORR, objective response rate. A: GEMOX + ICIs (sintilimab or camrelizumab) + lenvatinib B: GEMOX + ICIs(sintilimab or camrelizumab) + bevacizumab C:GEMOX + ICIs(sintilimab or camrelizumab)D:GEMOX

Table 3 Univariate and multivariate Cox analysis related to PFS

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*-Value	HR	95%CI	*P*-value
Age, < 60	1.185	0.724–1.942	0.499			
Gender, male	0.245	0.134–0.446	0.83			
CA199, < 37 U/m	1.243	0.628–2.357	0.188			
Combination regimen, chemotherapy	0.484	0.314–0.678	0.77			
Site of metastatic focus, one	0.48	0.295–0.780	0.003	0.442	0.271–0.719	0.001
Hepatic artery embolization with chemotherapy,	3.845	0.940–15.727	0.019	4.648	1.132–19.090	0.033
NLR < 2.30	-4.369	-4.305	< 0.001	-5.032	-5.49	< 0.001

HR Hazard Ratio, 95% *CI* 95% Confidence Interval, *P-Value* Probability Value, CA199, Carbohydrate Antigen 19–9, *U/m* Units per milliliter, *NLR* Neutrophil-to-Lymphocyte Ratio

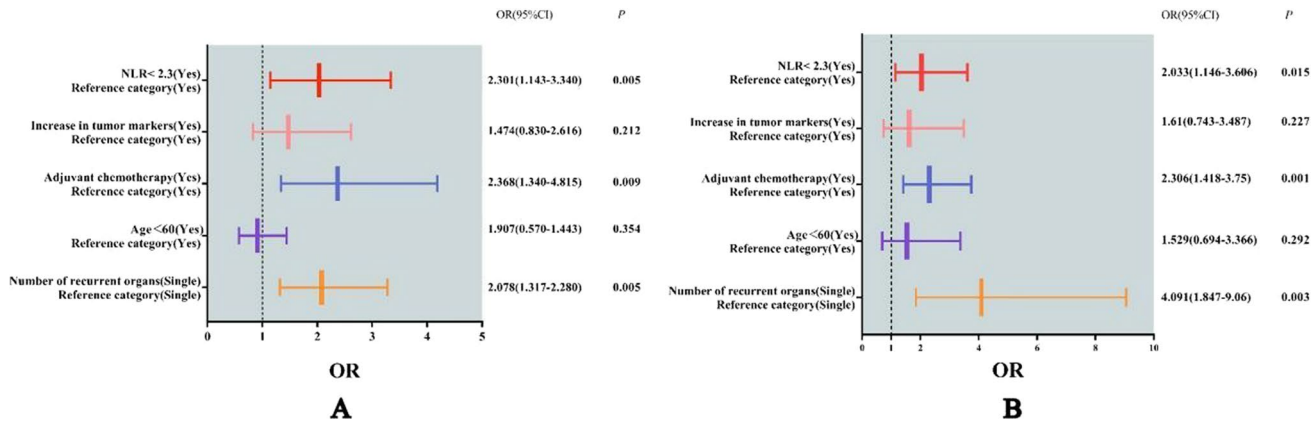


Fig. 5 **A** Forest plot of multifactorial risk profiles affecting PFS in group A. **B** Forest plot of multifactorial risk profiles affecting OS in group A. OR:odds ratio; *P*:*p*-value

Table 4 Univariate and multivariate Cox analyses related to OS

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*-Value	HR	95%CI	*P*-value
Age, < 60	1.305	0.401–4.245	0.659			
Gender, male	0.245	0.134–0.446	0.83			
CA199, < 37 U/m	1.954	0.432–8.812	0.384			
Combination regimen, chemotherapy	1.311	0.439–3.915	0.628			
Site of metastatic focus, one	0.419	0.257–0.687	0.001	0.436	0.266–0.713	0.001
Hepatic artery embolization with or without chemotherapy, yes vs no	5.152	1.257–21.112	0.023	4.858	1.183–19.950	0.028
NLR < 2.30vs ≥ 37	− 3.293	− 5.607 − 2.178	< 0.001	− 5.349	− 4.400 z − 2.297	< 0.001

Analysis of adverse reactions

Almost all patients had different types and degrees of TRAEs, and the total incidence was 97.9% (126/129), which were 96.0% (38/40), 97.9% (45/46), 96.7% (29/30), and 94.7% (53/56)in the group A, group B, group C, and group D, respectively. All TRAEs were mainly grade 1–2 level, with an incidence of 90.7% (117/129), mainly including 67.5% (87/129) of nausea and vomiting, 66.0% (85/129) of loss of appetite, 62.4% (80/129) of have the runs, etc. The total incidence of grade 3 level TRAEs was 18.6% (24/129), mainly including 6.8% (9/129) of spin, 5.4% (7/129) of fatigue, 5.15% (10/194) of skin and 3.9% (5/129) of hands and feet reactive, and so on (Table 5).

The incidence of grade 1–2 level AEs was 98.0% (39/40), 97.9% (45/46), 96.7% (29/30), and 96.4% (54/56) in the group A, group B, group C, and group D, respectively, while the incidence of grade 3level AEs was 10.0% (4/40), 19.6% (9/46), 40.0% (12/30), and 10.7% (6/56), respectively. The difference was not statistically significant ($P = 1.000$, $P = 3.020$, $P = 0.703$, and $P = 0.585$, respectively). In the group A, loss of appetite (13/40, 32.5%), nausea and vomiting (11/40, 28.0%), and hypothyroidism (11/40, 25.6%) were the common grade 1–2 level AEs, whereas fatigue (1/40, 4.0%), skin of hands and feet reactive (1/40, 4.0%), and spin (1/40, 4.0%) were common grade 3 level AEs. In the group B, have the runs (15/46, 32.6%) and immunohepatitis (10/46, 21.7%) were common grade 1–2 AEs, while spin (4/46, 7.0%) and skin of hands and feet reactive (3/46, 6.5%) were common grade 3 level AEs. Equally, in the group C, nausea and vomiting (14/30, 46.5%) and loss of appetite (10/30, 23.3%) were common grade 1–2 AEs, while immunohepatitis (6/30, 18.6%) and rashes (2/30, 7.0%) were common grade 3 level AEs. Finally, in the group D, fatigue (20/56, 37.2%) and hypothyroidism (13/56, 23.3%) were common grade 1–2 AEs, while myelosuppression (4/56, 7.0%) and fatigue (2/56, 3.8%) were common grade 3 level AEs (Table 5 and Figure 6).

Discussion

BTC is a lethal and highly malignant tumor with a low response rate and a poor prognosis. Compared to the published literature, this is the first study to assess the efficacy and safety of PD-1/PD-L1 (sintilimab or camrelizumab) inhibitors (sintilimab or camrelizumab) plus lenvatinib/bevacizumab with Gemox chemotherapy for patients with advanced BTC in the real world. Both treatment regimens showed a better antitumor activity than groups C and D (Figure 2 and Figure 4), with a median PFS of 12.42 months (95% CI:7.1–11.6), 11.05 months (95% CI:6.1–10.6), median OS of 13.63 months (95% CI:12.37–14.89), 12.41 months (95% CI:10.67–12.32), ORR of 45.00% (95% CI:31.8–56.7), 34.78% (95% CI:30.4–53.2), DCR of 87.50% (95% CI:81.1%–96.2%), and 78.26% (95% CI:76.1%–89.2%) in the group A and group B, respectively. Almost all patients (97.9%) experienced AEs; however, no grade 4 SAEs were reported, and 18.6% (24/129) of the patients experienced grade 3 AEs. The most common AE was nausea and vomiting (87/129, 67.5%), and the most common grade 3 AE was spin (9/129, 6.8%), which is acceptable, tolerable, and controllable. PD-1 inhibitors, which are important components of ICIs (sintilimab or camrelizumab), are increasingly used in BTC therapy [13–15]. Nivolumab combined with gemcitabine and tegafur chemotherapy has shown a good therapeutic effect in the first-line treatment of advanced BTC, with an ORR of 41.7% [14]. A study of PD-1 inhibitors plus lenvatinib for unresectable BTC showed an ORR of 42.1% [13]. These findings suggest that a combination of drugs with different mechanisms of action can overcome or improve the drug resistance of single-drug applications. Some studies suggest that chemotherapy may enhance the efficacy of PD-1 inhibitors through the following mechanisms: suppression of antitumor immunity by reducing myeloid-derived suppressor cells, selectively depleting monocytes/macrophages, enhancing the recruitment of antigen-presenting cells, and promoting the phagocytosis

Table 5 Treatment-related adverse events

Contents	A			B			C			D		
	(n = 40)			(n = 46)			(n = 30)			(n = 56)		
	All	Grade1-2	Grade3	All	Grade1-2	Grade3	All	Grade1-2	Grade3	All	Grade1-2	Grade3
Fatigue	5(11.6)	4(9.3)	1(4.0)	4(9.3)	3(7.0)	1(4.0)	8(18.6)	6(14.0)	2(4.7)	3(8.4)	16(37.2)	1(3.8)
High blood pressure	4(9.3)	4(9.3)	0(0.0)	6(14.0)	6(14.0)	0(0.0)	10(23.3)	10(23.3)	0(0.0)	8(18.6)	8(18.6)	0(0.0)
Pruritus	6(14.0)	6(14.0)	0(0.0)	4(9.3)	4(9.3)	0(0.0)	8(18.6)	8(18.6)	0(0.0)	9(20.9)	9(20.9)	0(0.0)
Rashes	4(9.3)	4(9.3)	0(0.0)	6(14.0)	6(14.0)	0(0.0)	7(16.3)	4(9.3)	3(7.0)	7(16.3)	7(16.3)	0(0.0)
Skin of hands and feet reactive	4(9.3)	3(7.0)	1(4.0)	10(23.3)	7(16.0)	9(20.0)	6(14.0)	5(11.6)	1(4.0)	6(14.0)	6(14.0)	0(0.0)
Loss of appetite	15(34.9)	14(32.56)	1(4.0)	4(9.3)	4(9.3)	3(7.0)	10(23.3)	10(23.3)	0(0.0)	10(23.3)	10(23.3)	0(0.0)
Nausea and vomiting	12(28.0)	12(28.0)	0(0.0)	4(9.3)	4(9.3)	0(0.0)	20(46.5)	20(46.5)	0(0.0)	15(34.6)	15(34.6)	0(0.0)
Insomnia	4(9.3)	4(9.3)	0(0.0)	3(7.0)	2(4.7)	0(0.0)	6(14.0)	6(14.0)	0(0.0)	8(18.6)	8(18.6)	0(0.0)
Have the runs	9(20.0)	9(20.0)	0(0.0)	15(34.9)	15(34.9)	0(0.0)	15(34.9)	15(34.9)	0(0.0)	10(23.3)	10(23.3)	0(0.0)
Spin	3(7.0)	2(4.7)	1(4.0)	5(11.6)	5(11.6)	3(7.0)	5(11.6)	5(11.6)	0(0.0)	9(20.0)	9(20.0)	0(0.0)
Myelosuppression	4(9.3)	4(9.3)	0(0.0)	3(7.0)	2(4.7)	0(0.0)	5(11.6)	5(11.6)	0(0.0)	10(23.3)	7(16.0)	3(7.0)
Elevated transaminases	7(16.0)	7(16.0)	0(0.0)	8(18.6)	8(18.6)	0(0.0)	10(23.3)	10(23.3)	0(0.0)	7(16.0)	7(16.0)	0(0.0)
Thyroid function Hypothyroidism	11(25.6)	11(25.6)	0(0.0)	7(16.0)	7(16.0)	0(0.0)	13(30.2)	11(25.6)	2(4.7)	10(23.3)	10(23.3)	0(0.0)
Immunohepatitis	4(9.3)	4(9.3)	0(0.0)	10(23.3)	10(23.3)	0(0.0)	11(25.6)	3(7.0)	8(18.6)	7(16.0)	7(16.0)	0(0.0)

of dendritic cells through cytokines produced by cytotoxic chemotherapy damage to cancer cells [16–18]. These studies showed that ICIs (sintilimab or camrelizumab) combined with the GEMOX regimen present improved efficacy. This aligns with our hypothesis, group C (combined immunotherapy) produced longer OS (11.23 months *vs* 8.86 months) and PFS (8.89 months *vs* 6.02 months) compared to group D.

Meanwhile, targeted therapy can reduce VEGF-mediated immunosuppression within the tumor and its microenvironment and may enhance anti–PD-1 and anti–programmed death ligand 1 (PD-L1) efficacy by reversing VEGF-mediated immunosuppression and promoting T-cell infiltration in tumors. Lenvatinib can promote the efficacy of immunotherapy by eliminating cancer cells through direct antitumor activity and immunogenic cell death and by reducing the number of cells targeted and destroyed by immune cells [19]. Bevacizumab knows how to bind to PD-L1 to prevent the interaction between PD-L1 and PD-1 and restore the immune system's ability to attack tumors. Immune cells can recognize and destroy cancer cells more efficiently, thus inhibiting the growth and spread of tumors [20]. A previous phase 2 clinical trial reported an ORR as high as 80% for patients with ICC treated with Gemox chemotherapy combined with the anti-PD1 antibody toripalimab and lenvatinib [17], but in our real-world study of patients with BTC, the ORR was only 45.00%. Our study has shown that 56.1% of the patients belonged to the non-first-line treatment, and the prompt application of the scheme has been confirmed for the first time to be aggravating, and the effect after application solutions is relatively poor. However, our treatment strategy brought a more substantial increase in median PFS (12.4 *vs*10.2 months). Additionally, another study reported an ORR of 56% for tislelizumab combined with lenvatinib and Gemox in potentially resectable locally advanced BTC [18]. A study of PD-1 inhibitors combined with hepatic arterial infusion in BTC reported an ORR of only 11.5% [21], suggesting that targeted therapy and immunotherapy combined with systemic chemotherapy have good efficacy in BTC. Besides, the study is the first large-sample research using bevacizumab as a targeted therapy for BTC, In 2004, AVF2107, the first phase 3 study evaluating bevacizumab in first-line treatment of mCRC demonstrated significantly longer survival of patients with the addition of bevacizumab to chemotherapy (irinotecan, fluorouracil, and leucovorin) compared to chemotherapy alone (10.6 vs 6.2 months, hazard ratio [HR] 0.66; $p < 0.001$) These results led to the approval of bevacizumab as the first targeted therapy for patients with mCRC [22, 23]. This aligns with our research, and compared to groups C and D, group B exhibited longer PFS and OS, as well as higher ORR and DCR (Table 2 and Figure 2).

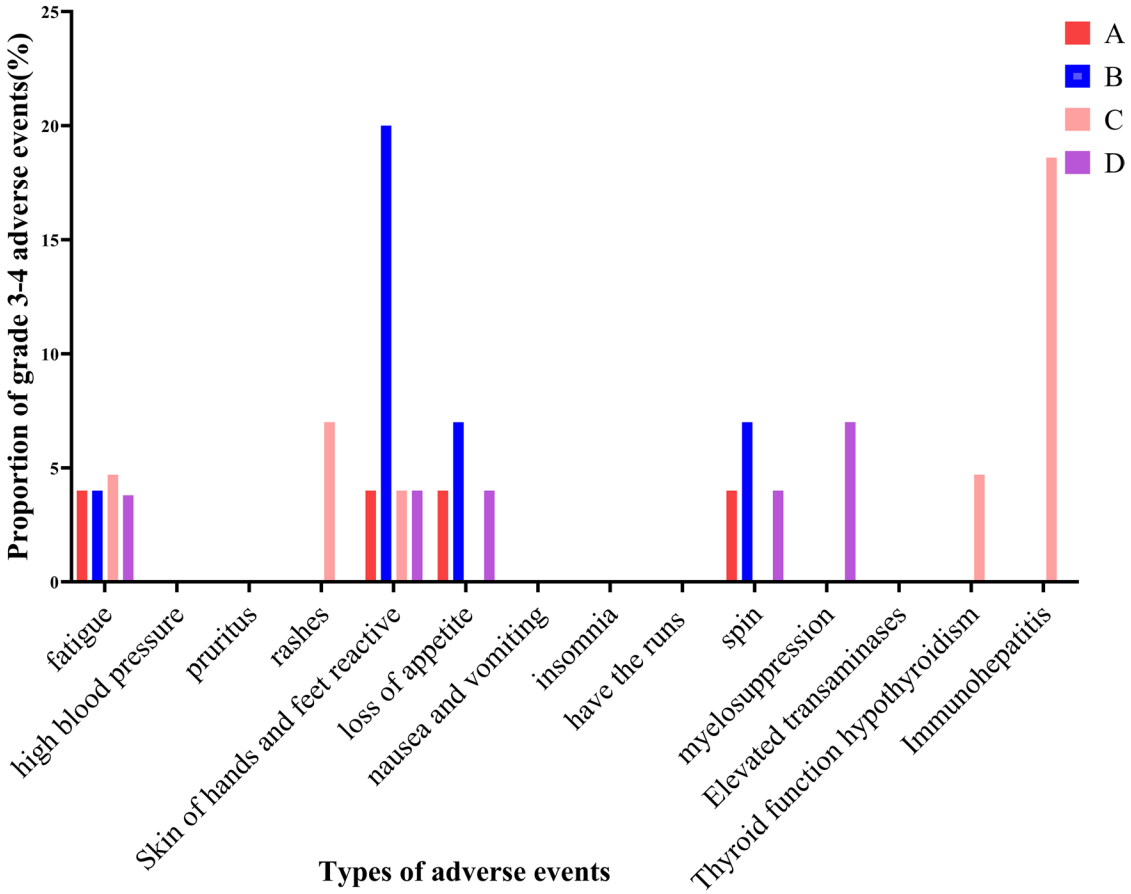
In the comparison between group A and B, group A seems to demonstrate a better antitumor activity. The median OS and median PFS in the group A were prolonged by 1.22 and 1.37 months compared with the group B, and the ORR and DCR improved by 10.22% and 9.54 % (according to the mRECIST criteria) and 21.3% and 11.7% (according to the RECIST1.1 criteria), respectively. We suspect that this may be related to adverse reactions such as hypertension induced by bevacizumab [24]. Besides, it also could be put in correlation with different target profiles, In fact, lenvatinib shows a more potent inhibitory activity against VEGF receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs), which both play a crucial suppressive role in immune responses. However, bevacizumab's effect is indirect, and it protects tumor new blood vessels by inhibiting vascular endothelial growth factor (VEGF) and subsequently inhibits cancer cell growth [25–27].

In addition, regression analysis revealed that patients' metastasis site, whether the neutrophil-lymphocyte ratio was < 2.3, and whether chemotherapy was administered through hepatic artery embolization and was related to patient prognosis. Multiple metastasis sites, NLR > 2.3, and chemotherapy was not administered through hepatic artery embolization were associated with a worse prognosis. This is consistent with multiple previous studies [31–33].

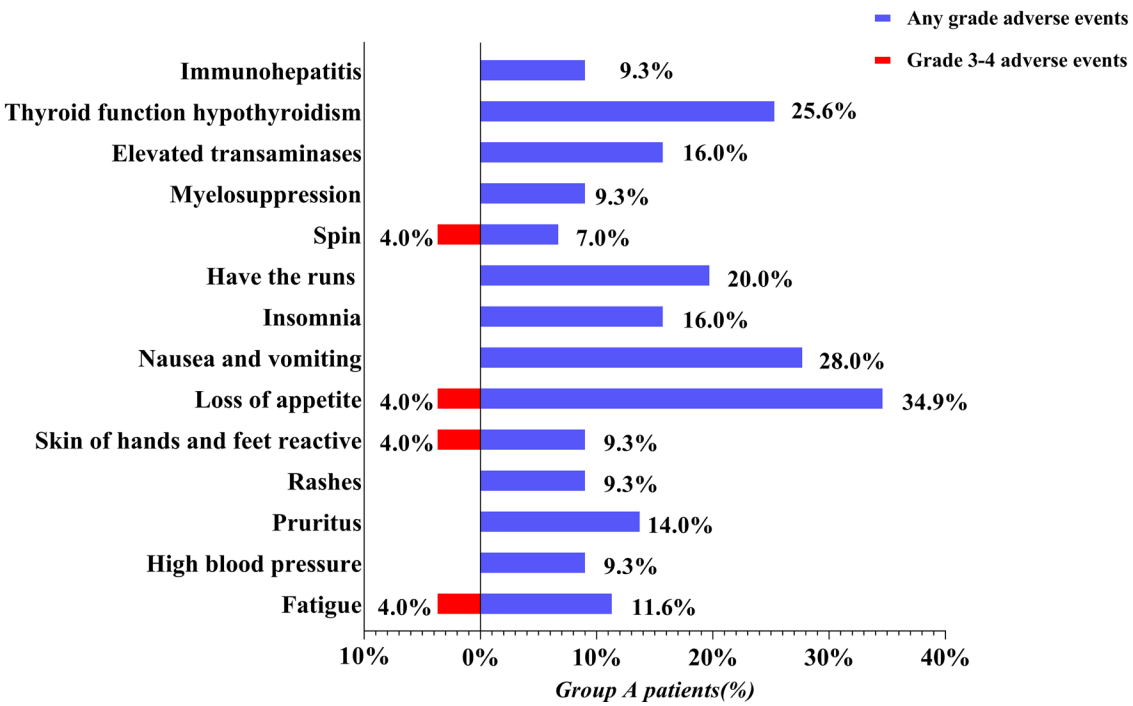
Among them, NLR is an independent factor affecting the prognosis of patients. Eliza W. Beal et al. found that elevated NLR was associated with poor prognosis after radical surgical resection of the BTC. Postoperative mOS was 17.5 months longer in patients with preoperative NLR ≤5 compared to those with NLR >5 (p<0.001) [34]. Thus, NLR >5 had been suggested to be an independent prognostic factor for GCA syndrome [35]. In our research, the PFS of patients with NLR <2.30 was 12.5 months, and the PFS of patients with NLR ≥2.30 was 7.4 months, the difference was 5.1 months which was also statistically significant (p=0.002).

Although targeted therapy and immunotherapy combined with chemotherapy resulted in more AEs, they were generally manageable. In our study, although almost all patients experienced varying degrees of AEs, no grade 4 AEs were observed. Approximately 18.6% (24/129) of the patients experienced grade 3 AEs. The most frequent AEs were 67.5% (87/129) of nausea and vomiting, 66.0% (85/129) of loss of appetite, 62.4% (80/129) of have the runs. The incidence of bone marrow suppression was higher in our study than that reported in other studies [28], which may be due to the use of chemotherapy in this study. Myelosuppression is a common adverse reaction to chemotherapy [29, 30]. In a cohort study of pembrolizumab combined with lenvatinib, the incidence of grades 3 and 4 AEs was 59.5% and 3.1% [28], respectively, suggesting that the addition of

(1)


Proportion of grade 3-4 adverse events(%)
25
20
15
10
5
0
A
B
C
D
fatigue
high blood pressure
pruritus
rashes
Skin of hands and feet reactive
loss of appetite
nausea and vomiting
insomnia
have the runs
spin
myelosuppression
Elevated transaminases
Thyroid function hypothyroidism
Immunohepatitis
Types of adverse events

(2)


Any grade adverse events
Grade 3-4 adverse events
Immunohepatitis 9.3%
Thyroid function hypothyroidism 25.6%
Elevated transaminases 16.0%
Myelosuppression 9.3%
Spin 4.0% 7.0%
Have the runs 20.0%
Insomnia 16.0%
Nausea and vomiting 28.0%
Loss of appetite 4.0% 34.9%
Skin of hands and feet reactive 4.0% 9.3%
Rashes 9.3%
Pruritus 14.0%
High blood pressure 9.3%
Fatigue 4.0% 11.6%
10% 0% 10% 20% 30% 40%
Group A patients(%)

◂**Fig. 6** (1) Frequency of grade 3/4 adverse events in all groups. (2) Frequency of any grade and grade 3/4 adverse events in Group A. A: GEMOX + ICIs(sintilimab or camrelizumab) + lenvatinib B:GEMOX + ICIs(sintilimab or camrelizumab) + bevacizumab C:GEMOX + ICIs(sintilimab or camrelizumab) D:GEMOX

chemotherapy to targeted therapy and immunotherapy does not increase the occurrence of AE in present study.

This study had some limitations. First, this was a single-center real-world study with small sample size; thus, the results should be interpreted with caution. In the future, more large-sample, multicenter, prospective studies are needed to confirm these results. Second, several immunotherapeutic drugs were used, including immunotherapy containing anti-PD-1 and anti-PD-L1regimens. Although there was no difference in the subgroup analysis in this study, and triple combined therapy with different immunotherapy agents all showed good ORR [17, 18], prospective studies with a single drug are still needed to confirm the differences in outcomes using different drug choices. Third, in the subgroup analysis, there was no difference in the tumor classification of BTC; however, few studies have reported that targeted therapy combined with immunotherapy and chemotherapy may be more effective in GBC and ICC than ECC [18], which needs to be confirmed by future studies on different pathological types. Finally, this is a retrospective, single-arm study, which lacks a control group with standard treatment regimens including chemotherapy. Prospective clinical trials are needed to remedy the shortcomings of the current study. Although this study has its limitations, as a real-world study, it can be used as a reference for the design of subsequent clinical research and the selection of clinical treatment strategies.

Conclusions

Lenvatinib/bevacizumab combined with PD-1/PD-L1 (sintilimab or camrelizumab) inhibitors (sintilimab or camrelizumab) and GEMOX in the first-line treatment of advanced biliary tract carcinoma is effective, safe, and well-tolerated in patients with advanced BTC. Further studies with larger prospective cohorts are warranted.

Author contribution Lu Zhao was contributed conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—original draft; and writing—review and editing. Zhengfeng Zhang was involved in data curation; investigation; visualization; and writing—original draft. Dazhen Wang was performed conceptualization; investigation; resources; and writing—original draft. Liu Yang was done conceptualization; resources; supervision; and writing—original draft. Ze Liu did conceptualization; resources; visualization; and writing—original draft.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and consent to participate This study was reviewed and approved by the Board of Directors of Harbin Medical University Cancer Hospital for inclusion in the review. Study participants provided written informed consent for the publication of any potentially identifiable image or data contained herein. The retrospective study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital prior to being performed (approval number is: KY2022-14). The study follows the World Medical Association Declaration of Helsinki.

Consent for publication All patients included in this study signed the Second Use Informed Consent for Historical Data/Biospecimens at Harbin Medical University-afliated Oncology Hospital.

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