Lenvatinib plus PD-1 inhibitors combined with chemotherapy versus lenvatinib plus PD-1 inhibitors for unresectable or recurrent biliary tract cancer

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Abstract

Background

Lenvatinib and programmed cell death-1 (PD-1) inhibitors have emerged as a novel treatment for patients with BTC. This study aimed to compare the efficacy and safety of triple therapy with lenvatinib, PD-1 inhibitors plus chemotherapy (LenP + C) and dual therapy with lenvatinib plus PD-1 inhibitors (LenP) in patients with unresectable or recurrent BTC.

Methods

BTC patients receiving LenP + C or LenP treatment between June 2020 and March 2022 were retrospectively analyzed. The primary outcome was progression-free survival (PFS). The secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety.

Results

Ninety-eight patients were included in the present study, and they were divided into the LenP + C group (n = 40) and LenP group (n = 58). The median PFS was 8.3 months in the LenP + C group, significantly longer than 4.5 months in the LenP group (HR = 0.471; 95% CI, 0.271–0.817; P = 0.007). Although no difference was found in ORR between the two groups (LenP + C, 42.5% vs. LenP, 27.6%, P = 0.125), the DCR was higher in the LenP + C group than in the LenP group (95.0% vs. 75.9%, P = 0.012). The median OS was comparable between the two groups (13.7 vs. 12.4 months, P = 0.749). Treatment-related adverse events were more frequently observed in the LenP + C group. The incidence of neutropenia (grade ⩾3) was higher in patients receiving triple therapy (15% vs. 2%, P = 0.035).

Conclusions

This study showed that treatment with lenvatinib and PD-1 inhibitors is safe and effective for advanced BTC. The combination of chemotherapy with lenvatinib and PD-1 inhibitors showed improved anti-tumor efficacy compared with lenvatinib and anti-PD-1 therapy, yet with more toxic effects.

1. Introduction

Biliary tract cancer (BTC) represents a heterogeneous group of cancers arising from bile duct epithelium and the gallbladder. Based on the anatomical location, BTC is classified into intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma and gallbladder cancer. Treatment of patients with BTC is challenging and unsatisfactory[1]. Although surgical resection is a curative treatment for BTC, most patients have unresectable disease at the time of diagnosis or relapse rapidly after surgery. For patients with unresectable or recurrent BTC, gemcitabine plus cisplatin is recommended as the standard first-line systemic therapy. However, the survival benefit with a median overall survival (OS) of less than one year is unsatisfactory[2, 3]. Other systemic treatment strategies with gemcitabine-based therapy, nab-Paclitaxel-based therapy, or platinum-based therapy, did not significantly improve the efficacy or patient survival[4–6].

Treatment strategies for BTC have evolved with the development of novel tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors[7–9]. In our previous prospective clinical trial (Chictr.org identifier: ChiCTR2100044476) and another two studies, the combination of lenvatinib and programmed cell death-1 (PD-1) inhibitors has shown promising therapeutic effects and tolerable adverse effects in advanced BTC, with an objective response rate (ORR) of 25-42.1% and disease control rate (DCR) of 76.3–83.9%[10–12]. With the comparable outcomes and safety of LenP to the standard first-line regimen (GC) in advanced BTC, it seemed that the dual therapy of lenvatinib and PD-1 Inhibitors is increasingly applied as an alternative regimen, particularly for the patients who cannot tolerate chemotherapy. Furthermore, several recent studies in BTC patients revealed that the combination of PD-1 or PDL-1 inhibitors and chemotherapy significantly improved the efficacy and survival outcome compared to chemotherapy alone[13–15]. However, the data on lenvatinib and PD-1 inhibitors combined with chemotherapy in the treatment of patients with advanced BTC are limited. Hence, we conducted this retrospective study to compare the combination of lenvatinib, PD-1 inhibitors plus chemotherapy with lenvatinib plus PD-1 inhibitors for unresectable or recurrent BTC.

2. Materials and Methods

2.1. Study Design and Patients

Between June 2020 and March 2022, the medical records of patients diagnosed with BTC who received lenvatinib plus PD-1 inhibitors or lenvatinib plus PD-1 inhibitors combined with chemotherapy (gemcitabine and cisplatin or gemcitabine and oxaliplatin) at the Second Affiliated Hospital of Zhejiang University were reviewed for eligibility. Patients were included based on the following criteria: a) at least 18 years of age; b)initially unresectable or recurrent BTC proven by pathology; c) at least one measurable target lesion; d) at least one cycle of systemic therapy and one evaluation of the tumor response in accordance with the Response Evaluation Criteria in Solid Tumors (RESIST) criteria (1.1); e) adequate hematologic, hepatic and renal functions; and f) Eastern Cooperative Oncology Group (ECOG) performance status score:0–1. Exclusion criteria included previous therapy of TKIs or PD-1 inhibitors or combined with other malignant tumors. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University. All patients provided written informed consent before inclusion.

2.2. Systemic Therapy

Lenvatinib was administered orally according to body weight (body weight ≥ 60 kg, 12 mg; <60 kg, 8 mg). PD-1 inhibitors were administered intravenously based on patient preference (pembrolizumab 200 mg, tislelizumab 200 mg, sintilimab 200 mg, camrelizumab 200 mg and toripalimab 240 mg every 3 weeks, and nivolumab 240 mg every 2 weeks). The chemotherapy regimens in the LenP + C group included: gemcitabine and cisplatin (GC) (n = 23, gemcitabine 1000 mg/m² and cisplatin 25 mg/m² on days 1 and 8 of a 3-week cycle); gemcitabine and oxaliplatin (GEMOX) (n = 17, gemcitabine 1000 mg/m² on days 1 and 8, and oxaliplatin 85 mg/m² on day 1 of a 3-week cycle). Treatment was continued until unacceptable toxicity, radiologically confirmed disease progression assessed by RECIST v1.1, tumor response for surgical conversion or withdrawal of consent.

2.3. Data Collection and Study Objectives

Baseline data included patient gender, age, Child-Pugh class, ECOG performance status, HBV infection, smoking history, PD-1 inhibitor types, primary tumor site, clinical TNM staging, pathology, histological differentiation, metastatic site and previous therapy. Imaging evaluation including enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and chest CT examination were performed at baseline and every 2–3 months during treatment. Based on RECIST criteria 1.1, objective tumor response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and was assessed by two professional clinicians according to the above imaging. Physical and laboratory examinations were performed within three days before each treatment. The data cutoff date was March 05, 2023

The primary endpoint was PFS. Secondary outcomes included ORR, DCR, OS and safety. ORR was calculated as the sum of CR and PR. DCR was calculated as the sum of CR, PR, and SD. PFS was defined as the time interval from treatment initiation to progression or death, or censored at the date of last follow-up in disease control. OS was defined as the time interval from treatment initiation to death from any cause, or censored at the date of last follow-up. Treatment-related adverse events (TRAEs) were evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.4. Statistical Analysis

Assessment of TRAEs was conducted in all patients who received at least one dose of lenvatinib plus PD-1 inhibitors or lenvatinib plus PD-1 inhibitors plus chemotherapy. Continuous variables were expressed as median (range) and between-group differences were compared using the Student's *t*-test or Mann Whitney U test. Categorical variables in the baseline characteristics were compared using the Pearson's c^2 test or Fisher's exact test. PFS and OS were estimated using the Kaplan-Meier method, and differences in the survival curves were analyzed by the log-rank test. All variables with a P value < 0.05 in univariate analyses were included in the multivariate analyses using Cox regression models. The hazard ratio (HR) and confidence intervals (CI) were calculated. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 26.0 software or GraphPad Prism software version 8.

3. Results

3.1. Patient Characteristics

Between June 2020 and March 2023, a total of 117 patients were screened for eligibility in this study, and 19 patients were excluded, including incomplete medical records (n = 4), no measurable lesions (n = 11), receiving previous tyrosine kinase inhibitor or PD-1 inhibitor (n = 3), and combining with other malignant tumors(n = 1). Ninety-eight patients who met the eligibility criteria were categorized into two treatment cohorts: 58 were in the lenvatinib plus anti-PD-1 group (LenP), and 40 were in the lenvatinib plus anti-PD-1 combined with

chemotherapy group (LenP + C) (Fig. 1). Twenty-four (41%) patients in the LenP group and twenty-four (60%) patients in the LenP + C group received lenvatinib plus PD-1 inhibitors as first-line therapy. The baseline characteristics are summarized in Table 1. The median age of the patients was 61.5(IQR, 52.8–69.5) years, 55 (56.1%) patients were female, 40 (40.8%) patients were ECOG performance status of 0, and the majority had a normal liver function and no viral infection. The most frequent primary disease was intrahepatic cholangiocarcinoma (56.1%). Most patients had metastatic disease (90.8%) with lymph nodes (77.6%) as the most frequent site of metastasis. In the LenP group, 30 (51.7%) of them had already received systemic chemotherapy, and 12 (20.7%) had received radical surgery resection. In the LenP + C group, 15 (37.5%) of them had received systemic chemotherapy, 7 (17.5%) had received radical surgery resection. The two treatment groups were well balanced regarding demographics and disease characteristics, with the exception of a higher rate of lymph node metastasis in the LenP + C group than in the LenP group (90.0% vs. 69.0%, P = 0.014).

Table 1
Patient Demographics and Baseline Characteristics ECOG, Eastern Cooperative Oncology Group; PTCD, percutaneous transhepatic cholangial drainage; HBV, hepatitis B virus; PD-1, programmed cell death protein-1; LenP, lenvatinib plus PD-1 inhibitor; LenP + C, lenvatinib plus PD-1 inhibitor in combination with chemotherapy

	LenP (n = 58)	LenP + C (n = 40)	*P* value
Gender			0.310
Male	23 (39.7%)	20 (50.0%)	
Female	35 (60.3%)	20 (50.0%)	
Age, median, years (IQR)	64.5 (52.8–71.5)	60.0 (52.0-68.8)	
< 65	29 (50.0%)	27 (67.5%)	0.085
>=65	29 (50.0%)	13 (32.5%)	
PD-1 inhibitor received			0.060
Tislelizumab	22 (37.9%)	21 (52.5%)	
Sintilimab	12 (20.7%)	12 (30.0%)	
Toripalimab	16 (27.6%)	3 (7.5%)	
Pembrolizumab	4 (6.9%)	4 (10.0%)	
Camrelizumab	2 (3.4%)	0 (0)	
Nivolumab	2 (3.4%)	0 (0)	
Line of treatment			0.070
First	24 (41.4%)	24 (60.0%)	
Second or above	34 (58.6%)	16 (40.0%)	
Previous therapy			
Systemic chemotherapy	30 (51.7%)	15 (37.5%)	0.165
Radical surgery resection	12 (20.7%)	7 (17.5%)	0.695
ECOG performance status			0.164
0	27 (46.6%)	13 (32.5%)	
1	31 (53.4%)	27 (67.5%)	
Child-Pugh			0.853
A	50 (86.2%)	35 (87.5%)	
B	8 (13.8%)	5 (12.5%)	
Hepatitis B virus infection	10 (17.2%)	9 (22.5%)	0.518
Smoking history	17 (29.3%)	12 (30.0%)	0.941
Primary tumor site			0.763
Intrahepatic	34 (58.6%)	21 (52.5%)	
Perihilar	7 (12.1%)	8 (20.0%)	
Distal	3 (5.2%)	2 (5.0%)	
Gallbladder	14 (24.1%)	9 (22.5%)	
TNM stage			0.174
II	6 (10.3%)	2 (5.0%)	

	LenP (n = 58)	LenP + C (n = 40)	*P* value
III	16 (27.6%)	18 (45.0%)	
IV	36 (62.1%)	20 (50.0%)	
Pathology			1.000
Adenocarcinoma	57 (98.3%)	39 (97.5%)	
Squamous cell carcinoma	1 (1.7%)	1 (2.5%)	
Histological differentiation			0.847
Well	4 (6.9%)	2 (5.0%)	
Moderate	15 (25.9%)	9 (22.5%)	
Poor	26 (44.8%)	17 (42.5%)	
Unknown	13 (22.4%)	12 (30.0%)	
Extent of disease			
Metastatic	50 (86.2%)	39 (97.5%)	0.122
Recurrent	18 (31.0%)	7 (17.5%)	0.131
Metastatic site			
Lymph node	40 (69.0%)	36 (90.0%)	0.014
Liver	27 (46.6%)	16 (40.0%)	0.521
Lung	8 (13.8%)	2 (5.0%)	0.283
Peritoneum	9 (15.5%)	3 (7.5%)	0.381
Bone	4 (6.7%)	5 (12.5%)	0.318

3.2. Efficacy

The data cutoff date was March 05, 2023, and the median follow-up was 12.8 months (IQR 8.7–20.3 months). The median PFS was 4.5 (95% CI, 3.7–5.4) months in the LenP group and 8.3 (95% CI, 5.2–11.5) months in the LenP + C group (HR = 0.471; 95% CI, 0.271–0.817; P = 0.007; Fig. 2). The 6-month PFS rates were 42.0% in the LenP and 54.6% in the LenP + C group. There was no difference in OS between the groups, with a median of 12.4 (95% CI, 9.2–15.6) months in the LenP group vs. 13.7 (95% CI, 9.6–17.8) months in the LenP + C group (HR = 0.928; 95% CI, 0.588–1.466; P = 0.749; Fig. 2). The 1-year OS rates were 53.4% in the LenP and 64.8% in the LenP + C group.

The treatment response is summarized in Table 2. Based on the RECIST v1.1 criteria, we found that the DCR was higher in the LenP + C group than in the LenP group (95.0% vs. 75.9%, P = 0.012). However, there was no significant difference in ORR between the two groups (LenP + C, 42.5% vs. LenP, 27.6%, P = 0.125). A complete response (CR) was achieved in 1 patient in the LenP + C group. Ten (17.2%) patients in the LenP group and 9 (22.5%) patients in the LenP + C group successfully converted to surgery. The median conversion time from initiation of systemic therapy to surgery was 4.6 (IQR, 3.0-6.9) months in the LenP group and 4.3 (IQR, 2.9–4.7) months in the LenP + C group. With regards to tumor regression, 67.2% (39/58) of patients in the LenP group, and 82.5% (33/40) of patients in the LenP + C group experienced a decrease in the sum of target lesions from baseline (Fig. 3). The median best percentage change from baseline was − 15.5% (-100.0% to + 80.0%) in the LenP group and − 25.4% (-100% to + 51.7%) in the LenP + C group. Median treatment duration of the LenP and LenP + C groups were 3.8 (IQR, 2.3-6.0) months and 4.8 (IQR, 3.1–8.5) months, respectively. At the data cutoff date, no patients remained on study treatment, and 8 patients in the LenP group and 9 patients in the LenP + C group were still alive.

Table 2
Summary of tumor response and survival outcomes

Response*	LenP (n = 58)	LenP + C (n = 40)	*P* value
Overall response, n (%)			0.028
CR	0	1 (2.5%)	
PR	16(27.6%)	16 (40.0%)	
SD	28(48.3%)	21 (52.5%)	
PD	14 (24.1%)	2 (5.0%)	
Objective response, n (%)	16(27.6%)	17 (42.5%)	0.125
Disease control, n (%)	44(75.9%)	38 (95.0%)	0.012
PFS, months, median (95%CI)	4.5(3.7–5.4)	8.3 (5.2–11.5)	0.006
6-month PFS rate	42.0%	54.6%	
OS, months, median (95%CI)	12.4(9.2–15.6)	13.7 (9.6–17.8)	0.749
1-year OS rate	53.4%	64.8%	
Surgical conversion, n (%)	10(17.2%)	9 (22.5%)	0.518
Conversion time, months, median (IQR)	4.6(3.0-6.9)	4.3 (2.9–4.7)	0.265

*Treatment response was evaluated according to RECIST v1.1. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

The results of univariate and multivariate analyses of PFS and OS are listed in Table 3. Multivariate analysis showed that independent risk factors for PFS were the method of treatment (LenP vs. LenP + C, HR = 0.393; 95% CI, 0.223–0.695; P = 0.001), Child-Pugh class (A vs. B, HR = 2.268; 95% CI, 1.067–4.825; P = 0.033), primary tumor site (Distal vs. Intrahepatic, HR = 6.613; 95% CI, 2.333–18.751; P < 0.001) and ECOG (0 vs. 1, HR = 2.663; 95% CI, 1.384–5.121; P = 0.003). Furthermore, independent risk factor for OS was ECOG (0 vs. 1, HR = 1.637; 95% CI, 1.013–2.645; P = 0.044).

Table 3
Univariate and multivariate analyses of risk factors for progression-free survival and overall survival

Variable	PFS						OS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender, (male/female)	1.474	0.870–2.495	0.149				1.410	0.902–2.204	0.132			
Age(y)	1.003	0.981–1.025	0.815				1.022	1.001–1.042	0.038	1.018	0.997–1.039	0.087
Child-Pugh (A/B)	2.418	1.267–4.615	0.007	2.268	1.067–4.825	0.033	2.158	1.160–4.016	0.015	1.502	0.772–2.922	0.231
ECOG (0/1)	2.646	1.452–4.821	0.001	2.663	1.384–5.121	0.003	1.801	1.143–2.838	0.011	1.637	1.013–2.645	0.044
Treatment (LenP/LenP + C)	0.471	0.271–0.817	0.007	0.393	0.223–0.695	0.001	0.928	0.588–1.466	0.750			
Hepatitis B virus infection (no/yes)	0.641	0.303–1.357	0.245				0.869	0.487–1.551	0.635			
Smoking history (no/yes)	0.870	0.499–1.516	0.623				0.664	0.406–1.086	0.103			
Line of treatment (first/second or above)	1.381	0.816–2.335	0.229				1.321	0.852–2.048	0.213			
Primary tumor site			0.001			0.003			0.217			
Intrahepatic	1.000			1.000			1.000					
Perihilar	1.426	0.720–2.821	0.309	0.932	0.432–2.001	0.858	0.827	0.476–1.811	0.889			
Distal	8.327	3.001–23.104	< 0.001	6.613	2.333–18.751	< 0.001	2.465	0.957–6.353	0.062			
Gallbladder	1.986	1.022–3.860	0.043	1.866	0.941-3.700	0.074	1.314	0.780–2.214	0.305			
TNM stage			0.863						0.093			
II	1.000						1.000					
III	1.345	0.449–4.027	0.596				3.605	1.089–11.936	0.036			
IV	1.311	0.466–3.690	0.608				2.760	0.859–8.869	0.088			
Histological differentiation			0.484						0.294			
Well	1.000						1.000					
Moderate	2.617	0.724–9.460	0.142				0.915	0.364-2.300	0.851			
Poor	1.942	0.576–6.548	0.285				0.597	0.249–1.433	0.248			
Unknown	1.793	0.521–6.172	0.355				0.917	0.371–2.268	0.852			
Extent of disease												
Metastatic (no/yes)	1.122	0.442–2.846	0.809				1.467	0.636–3.385	0.369			

Variable	PFS			OS		
Recurrent (no/yes)	0.896	0.509–1.578	0.704	0.831	0.492–1.404	0.489
Metastatic site						
Liver	1.320	0.794–2.195	0.284	1.073	0.692–1.665	0.753
Lung	0.667	0.300-1.483	0.321	0.838	0.418–1.678	0.617
Peritoneum	1.176	0.574–2.411	0.658	1.441	0.780–2.665	0.244
Lymph node	1.100	0.609–1.986	0.753	1.243	0.717–2.155	0.438
Previous therapy(no/yes)						
Radical surgery resection	0.920	0.527–1.605	0.769	0.899	0.532–1.518	0.689
Systemic chemotherapy	1.098	0.644–1.874	0.731	1.136	0.648–1.992	0.657
Transarterial chemoembolization	1.227	0.296–5.085	0.778	0.704	0.176–2.875	0.625
Regional radiotherapy	1.003	0.356–2.830	0.995	0.930	0.292–2.964	0.902

3.3. Safety

Treatment-related adverse events (TRAEs) occurred in all patients in the study (Table 4). Any grades of TRAEs were more frequent in the LenP + C group than in the LenP group: neutropenia [29 (73%) vs. 27 (47%), P = 0.011], anemia [31 (78%) vs. 21 (36%), P < 0.001], thrombocytopenia [26 (65%) vs. 18 (31%), P = 0.001], nausea/vomiting [20 (50%) vs. 14 (24%), P = 0.008], and fever [13 (33%) vs. 3 (5%), P < 0.001]. The most common grade ⩾3 adverse events were elevated ALT/AST (16%) and rash (9%) in the LenP group, while elevated ALT/AST (20%), neutropenia (15%) and thrombocytopenia (13%) were most frequently observed in the LenP + C group. The incidence of grade ⩾3 neutropenia was higher in the LenP + C group than in the LenP group [6 (15%) vs. 1(2%), P = 0.035]. Treatment-related death due to autoimmune myocarditis occurred in one patient in the LenP group.

Table 4
Treatment-related adverse events

	Any grade			Grade > = 3		
	LenP (n = 58)	LenP + C (n = 40)	*P* value	LenP (n = 58)	LenP + C (n = 40)	*P* value
Elevated ALT/AST	39 (67%)	26 (65%)	0.818	9 (16%)	8 (20%)	0.565
Neutropenia	27 (47%)	29 (73%)	0.011	1 (2%)	6 (15%)	0.035
Anaemia	21 (36%)	31 (78%)	< 0.001	0 (0)	1 (3%)	0.408
Thrombocytopenia	18 (31%)	26 (65%)	0.001	3 (5%)	5 (13%)	0.354
Fatigue	20 (35%)	15 (38%)	0.759	1 (2%)	0 (0)	1.000
Hypertension	17 (29%)	13 (33%)	0.736	3 (5%)	1 (3%)	0.890
Nausea/Vomiting	14 (24%)	20 (50%)	0.008	0 (0)	0 (0)	1.000
Fever	3 (5%)	13 (33%)	< 0.001	0 (0)	1 (3%)	0.408
Rash	14 (24%)	14 (35%)	0.242	5 (9%)	3 (8%)	1.000
Peripheral sensory neuropathy	8 (14%)	10 (25%)	0.159	0 (0)	0 (0)	1.000
Palmar-plantar erythrodysaesthesia	9 (16%)	7 (18%)	0.675	0 (0)	0 (0)	1.000
Stomatitis	9 (16%)	5 (13%)	0.724	0 (0)	1 (3%)	0.408
Decreased appetite	9 (16%)	8 (20%)	0.585	0 (0)	0 (0)	1.000
Diarrhea	6 (10%)	5 (13%)	0.740	0 (0)	0 (0)	1.000
Hypothyroidism	5 (9%)	3 (8%)	1.000	0 (0)	0 (0)	1.000
Proteinuria	5 (9%)	4 (10%)	1.000	0 (0)	0 (0)	1.000
Pruritus	3 (5%)	5 (13%)	0.354	0 (0)	0 (0)	1.000
Hepatic encephalopathy	3 (5%)	2 (5%)	1.000	1 (2%)	1 (3%)	1.000
Ischaemic stroke	0 (0)	1 (3%)	0.408	0 (0)	1 (3%)	0.408
Autoimmune myocarditis	1 (2%)	1 (3%)	1.000	1 (2%)	1 (3%)	1.000

4. Discussion

This retrospective study evaluated the efficacy and safety of lenvatinib and anti-PD-1 therapy with or without the combination of chemotherapy in patients with unresectable or recurrent BTC. We found that the combination of chemotherapy with lenvatinib and PD-1 inhibitors might exert a better anti-tumor effect and lead to a longer PFS. Although the combination therapy increased the frequency of TRAEs, they were mostly controllable. These findings provide evidence for future large prospective randomized clinical studies of this combination therapy for the treatment of advanced BTC.

Surgical resection is a curative treatment for patients with resectable BTC; however, there are few therapeutic options for unresectable or recurrent patients. Chemotherapy such as the GC or GS regimen is recommended as the standard of care for advanced BTC, yet high toxicity of this regimen can lead to poor tolerance. The development of novel TKIs and immune checkpoint inhibitors brought new treatment options for advanced BTC. A recent study analyzing the therapeutic outcomes of lenvatinib and PD-1 inhibitors in advanced BTC achieved a median PFS of 4.9 months and OS of 11.0 months[10]. Our previous phase II study using lenvatinib and PD-1 inhibitors as first-line treatment to treat unresectable BTC reported that the median PFS was 8.0 months and OS was 17.7 months[11]. In the present study, the median PFS was 4.5 months and OS was 12.4 months among the patients receiving lenvatinib and PD-1 inhibitors, which were consistent with the results reported in previous studies. These findings indicate that combination therapy with TKIs and PD-1 inhibitors can achieve a promising survival outcome, suggesting that it may be a potential treatment strategy for advanced BTC, especially for the patients cannot tolerate or refuse standard chemotherapy.

Combined therapy with immune checkpoint inhibitors and chemotherapy has been investigated in advanced BTC. Several studies have shown that the combination of anti-PD-1 antibodies and chemotherapy significantly improved the PFS and OS (PFS, 4.2 to 6.1 months; OS, 11.8 to 15.4 months) compared to anti-PD-1 monotherapy or chemotherapy alone[13, 14, 16, 17]. However, reports on triple therapy with TKIs, PD-1 inhibitors and chemotherapy for the treatment of BTC are scarce. Recently, a series demonstrated that lenvatinib plus PD-1 inhibitors in combination with locoregional chemotherapy was associated with a significantly better tumor response and survival benefits in patients with advanced hepatocellular carcinoma[18–20]. These patients achieved an ORR of 40-80.6% and DCR of 77.6–93.5%. These promising results encouraged us to investigate the efficacy of triple therapy with lenvatinib, PD-1 inhibitors and chemotherapy in BTC patients. A phase 2 clinical trial of GEMOX chemotherapy in combination with anti-PD1 antibody and lenvatinib for advanced intrahepatic cholangiocarcinoma reported robust anti-tumor efficacy of the triple therapy with an ORR of 80% and DCR of 93.3%[21].

In the present study, we compared the efficacy of triple therapy (lenvatinib, PD-1 inhibitors plus chemotherapy) with dual therapy (lenvatinib plus PD-1 inhibitors). Patients enrolled in this study had relatively late-stage disease and the majority had metastases or poorly differentiated adenocarcinoma. Among the 40 patients receiving triple therapy, one achieved a CR, 16 PR, 21 SD, and yielded an ORR of 42.5% and DCR of 95.0%. The study showed that patients receiving triple therapy exhibited a better median PFS (8.3 vs. 4.5 months) and DCR (95.0% vs. 75.9%) compared to those receiving dual therapy. Although no significant difference in ORR was found, it was relatively high in patients treated with triple therapy (42.5%) compared to 27.6% in the LenP group. With regards to tumor regression, tumor size reduction was observed in 82.5% of patients receiving triple therapy, compared with 67.2% in the LenP group. Taken together, these results suggest that triple therapy with lenvatinib, PD-1 inhibitors plus chemotherapy was effective in advanced BTC. However, better anti-tumor efficacy did not translate into longer survival. The median OS was 13.7 months in the LenP + C group and 12.4 months in the LenP group, respectively. This may be due to the following reasons: Radical resection is considered the only curative treatment for BTC; however, surgical conversion was similar between the two groups (LenP + C, 22.5% vs. LenP, 17.2%). Secondly, the difference in later-line therapy after failure to each treatment also impacted the OS. In the present study, 22 patients in the LenP + C group and 39 patients in the LenP group underwent disease progression at the data cutoff. However, only 4 (18.1%) patients in the LenP + C group received later-line systemic therapy, compared to 19 (48.7%) patients in the LenP group. Thirdly, a more intensive therapy is usually associated with more toxic effects. The incidences of any grade and grade ⩾3 TRAEs were higher in patients receiving triple therapy compared to dual therapy, which might also influence the OS of the patients in the LenP + C group.

The efficacy benefit observed in the present study might be attributed to the synergistic anti-tumor effect of lenvatinib, PD-1 inhibitors and chemotherapy. Lenvatinib is an anti-angiogenic agent, and preclinical data revealed that it can also improve the anti-tumor efficacy of immunotherapy targeting PD-1/PD-L1 by enhancing the activity of T lymphocytes[22, 23]. PD-1 inhibitors magnify the anti-tumor activity of T lymphocytes by blocking the negative regulatory signaling of PD-1/PD-L1[24]. Chemotherapy exerts an anti-tumor effect by cytotoxicity; however, increasing evidence has indicated that chemotherapy can enhance the anti-tumor efficacy of immunotherapy by increasing antigen presentation and T lymphocyte recruitment[25]. Taken together, the synergistic effects of triple therapy exhibit a better tumor response.

In terms of safety, the most frequent TRAEs in the present study were liver function injury and hematological toxicities. Any grade of neutropenia, anemia, thrombocytopenia, nausea/vomiting, fever and grade ⩾3 neutropenia significantly increased in the LenP + C group, which might be attributed to the chemotherapy[26, 27]. Although triple therapy was associated with more TRAEs, they were generally controllable. Treatment-related death occurred in one patient receiving lenvatinib and PD-1 inhibitors. The cause of death was autoimmune myocarditis, which was considered an immune-related adverse effect and is consistent with reports from previous studies[28, 29].

This study had several limitations. First, this was a retrospective study with a small sample size, which may have led to selection bias. Second, the anti-PD-1 antibodies used in this study were not unified. Therefore, well-designed randomized controlled trials with a specified therapeutic regimen are needed to verify the benefits of triple therapy in BTC patients.

5. Conclusions

Treatment with lenvatinib and PD-1 inhibitors showed promising effects in advanced BTC. Compared to lenvatinib and PD-1 inhibitors, the combination of chemotherapy with lenvatinib and PD-1 inhibitors was associated with a significantly better antitumor response and higher toxicity in patients with unresectable or recurrent BTC. Randomized controlled trials are required to further confirm the benefit of this combination therapy.

Declarations

Author Contributions: ZX and J-ZD wrote the manuscript. J-ZD, ZX, S-ZW, ZB, L-GG, Z-QY, G-ZZ and Z-YB collected, analyzed and interpreted the data. YS and ZX designed the research and supervised the report. All authors contributed to the article and approved the submitted version.

Statement of ethics: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of the Second Affiliated Hospital of Zhejiang University of Medicine (NO.20220492) and informed consent was obtained from all individual participants. All participants were asked to provide written informed consent.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Figures

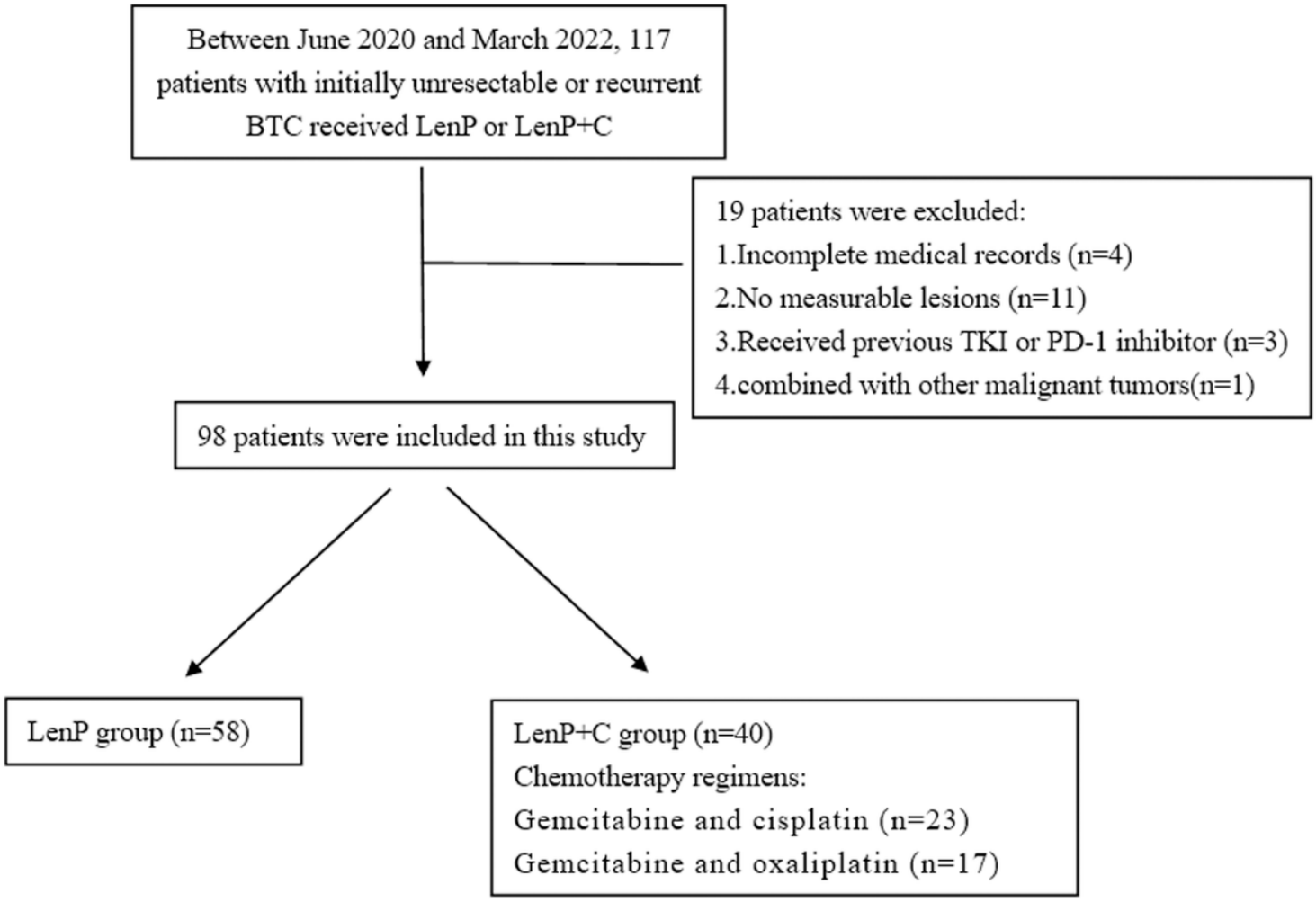

Figure 1

Flow chart of patient inclusion. Between June 2020 and March 2022, 117 patients with unresectable or recurrent BTC receiving LenP or LenP+C therapy were screened for eligibility. Ninety-eight patients were included, with 58 patients in the LenP group and 40 patients in the LenP+C group.

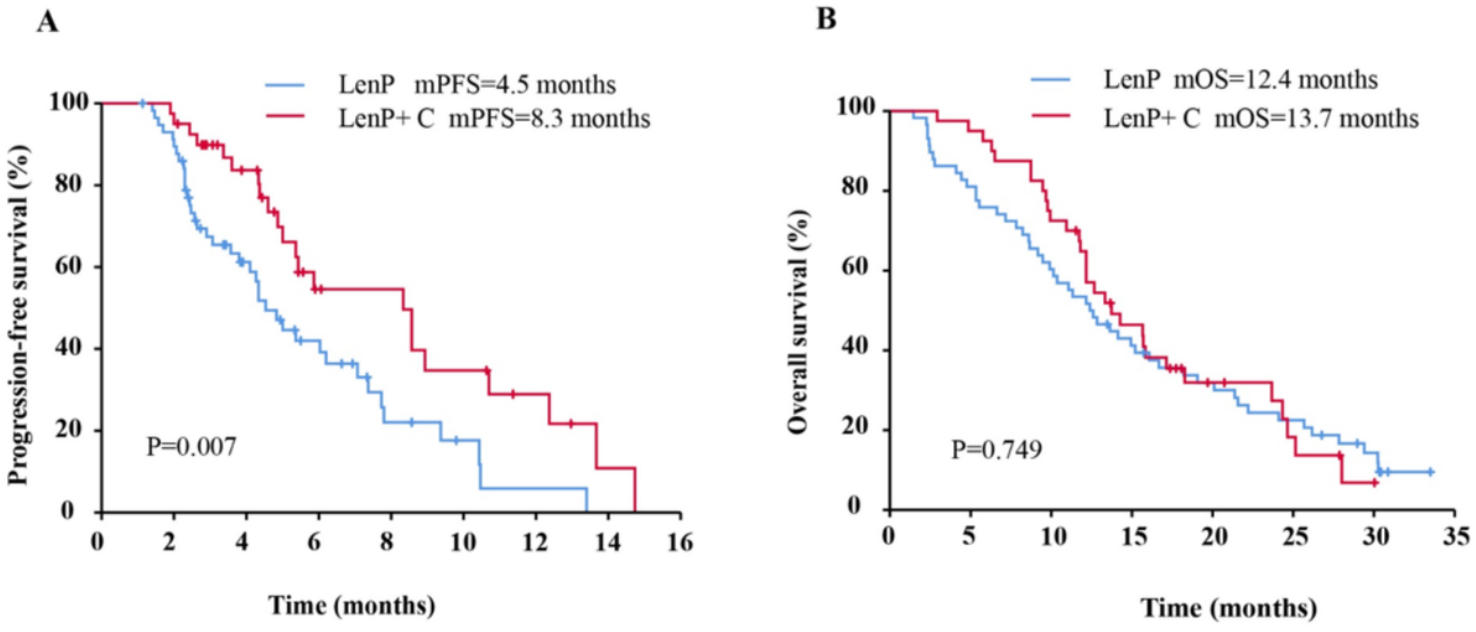

Figure 2

Kaplan-Meier curves of survival outcomes of patients in the two groups. (A) Kaplan-Meier estimation of progression-free survival of the two groups. (B) Kaplan-Meier estimation of overall survival of the two groups.

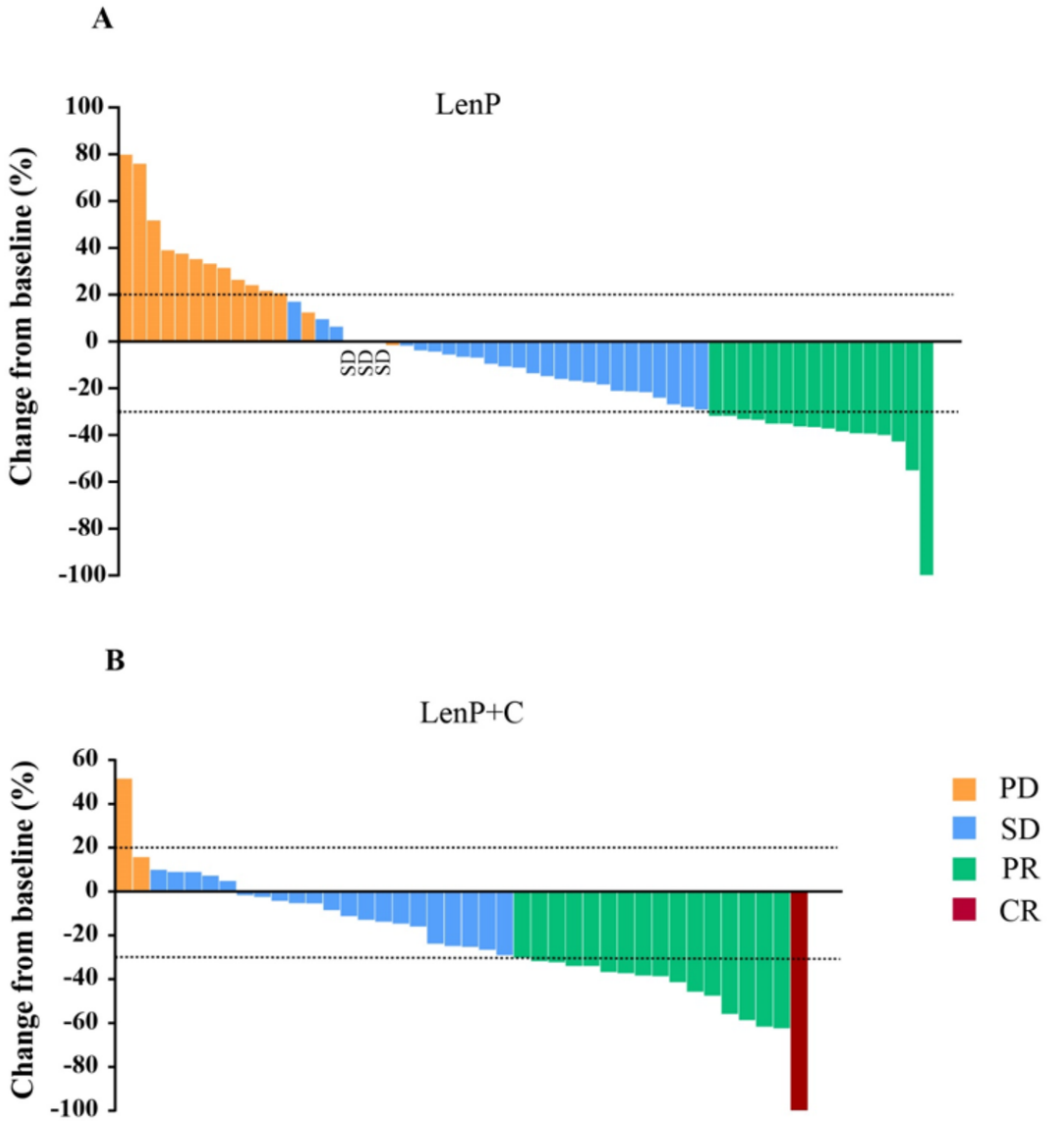

Figure 3

Anti-tumor efficacy of the two therapeutic regimens in patients with unresectable or recurrent biliary tract carcinoma. Waterfall plot of maximum percent change in tumor size from baseline for individual patients in the LenP group (A) and LenP+C group (B).