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Apatinib Monotherapy as a Second-Line Treatment for Patients with Advanced Biliary Tract Cancer: a Retrospective Single-Center Observational Study

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Abstract

Biliary tract cancer is an aggressive gastrointestinal malignancy with a dismal prognosis. Combined chemotherapy with gemcitabine and cisplatin is the gold standard of first-line treatment for patients with advanced biliary tract cancer, while second-line therapy remains inconclusive. We aimed to evaluate the effects of apatinib as a second-line regimen in patients with advanced biliary tract cancer. We retrospectively analyzed 18 patients with advanced biliary tract cancer who failed first-line therapy with gemcitabine alone or gemcitabine combined with cisplatin and received second-line treatment with apatinib from June 2016 to October 2017. Adverse events, progression-free survival, objective response rate, and disease control rate were documented and evaluated. All patients were followed up until progression of the disease. All patients were included in the efficacy analysis, including 6 drop-out cases. The 1-month tumor response assessment showed an objective response rate of 33% and a disease control rate of 72%. At a 6-month follow-up, a disease control rate of 44% was observed. The cohort achieved a median progression-free survival of 8 months; for gallbladder carcinoma of 2.5 months; for cholangiocarcinoma of 8 months. Fatigue, hypertension, and proteinuria were the most frequently occurring apatinib-related toxicities. Nine cases of grade 3 adverse effects were recorded, and no bleeding cases or treatment-related death were observed. This retrospective analysis showed favorable outcome and manageable toxicities of apatinib treatment in a second-line setting in patients with advanced biliary tract cancer. Perspective studies are needed to confirm the results from this study.

Keywords: Apatinib mesylate; second-line treatment; biliary-tract cancer; targeted therapy; anti-angiogenesis

Abbreviations: BTC: Biliary tract cancer

What's New: This is the first report to demonstrate that Apatinib may have a beneficial effect in patients with advanced biliary tract cancer in a second-line setting. The result shows a progressive-free survival of 8 months, which provides a rational for further perspective study.

Introduction

Biliary tract cancer (BTC) is a lethal malignancy encompassing gallbladder carcinoma and cholangiocarcinoma. The latter is further subdivided into intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma [1]. Though it is less common in the Western world, where the annual incidence is 0.35 to 2 per 100,000, the prevalence in Hispanic and Asian populations is much higher [2]. For instance, the incidence may be up 40-fold higher in China than in the United Kingdom [3,4].

At present, a satisfactory outcome of BTC hinges on early diagnosis and complete surgical resection. However, due to its slow-growing nature and non-specific symptomatology, BTC is often diagnosed at an advanced stage when surgical options are limited [5,6]. Even in patients undergoing successful resection, recurrence rates may reach 49-64%, and most cases will eventually progress to metastatic disease, which highlighting the importance of advancing adjuvant therapies [7-9].

According to the guideline of the National Comprehensive Cancer Network, Version 2.2019, standard first-line chemotherapeutic regimens for BTC include gemcitabine-based or gemcitabine-cisplatin combination therapy for the metastatic or unresectable disease [10]. However, no clear guidance exists for second-line treatment following disease progression under first-line chemotherapy. Many clinical trials are currently being conducted to evaluate the efficacy of a multitude of agents targeting the molecular level in second-line settings [11]. However, the results of these trials have not yet been published. Angiogenesis, a physiological process through which new blood vessels form from pre- existing vessels is responsible for tumor growth and disease progression [12, 13]. In recent years, anti-angiogenic treatment has become an essential tool in the armamentarium against advanced cancers. Vascular endothelial growth factor (VEGF) and its cognate receptor, VEGFR-2 is recognized as the most prominent regulators of angiogenesis [14], and have therefore become the main target of current antiangiogenic agents. Thus, strategies focus on antiangiogenesis therapy via VEGF pathway inhibition might have clinical benefits in the treatment of patients with advanced BTC [15]. A number of agents targeting the VEGF/VEGFR signaling pathway, including bevacizumab, aflibercept, and ramucirumab, have been developed and approved for several indications by the U.S. Food and Drug Administration [13]. VEGF is over expressed in 40-75% of patients with BTC [16]. In a phase II trial, bevacizumab was added to second-line chemotherapy for advanced BTC and reported to have a modest benefit as well as a tolerable safety profile [17]. Moreover, in another phase II trial of treatment of advanced BTC, ramu-

cirumab showed limited activity but still infrequent grade 3-4 treatment-related adverse events (AEs) when combined with pembrolizumab in a second-line setting [18].

Apatinib is an oral tyrosine kinase inhibitor selectively inhibiting VEGFR-2, thereby suppressing tumor growth by obstructing angiogenesis. It has been approved in China for advanced or metastatic gastric cancer and has shown promising therapeutic effects against a variety of other cancer types, including ovarian cancer [19], breast cancer [20-22], lung cancer [23, 24], hepatocellular carcinoma [25-27], sarcoma [28-30], and thyroid cancer [31,32]. Nevertheless, research evaluating the effect of apatinib on advanced BTC is limited. As a broad-spectrum anticancer agent, apatinib has been a frequent option for patients with advanced BTC after first-line treatment failure in our hospital at the discretion of the treating physicians and showed favorable effects.

In the present study, we hypothesized that apatinib is an effective second-line regimen for the treatment of patients with advanced BTC. Therefore, we retrospectively assessed the effects of apatinib monotherapy in a second-line setting after the failure of first-line systemic chemotherapy with gemcitabine or gemcitabine-cisplatin in patients with advanced BTC. 98

Patients and Methods

Eligibility criteria

The study was conducted retrospectively on patients treated between June 2016 and October 2017 at Qinhuangdao Fourth Hospital, China. Eligibility criteria included 1) age>18 years old, 2) pathologically confirmed advanced BTC with contrast-enhanced CT or magnetic resonance imaging (MRI) scan, 3) disease progressed after first-line chemotherapy – gemcitabine or gemcitabine-cisplatin, 4) started apatinib monotherapy as second-line regimen after first-line failure, 5) Karnofsky Performance Scale (KPS) >80. Key exclusion criteria were: pregnant or lactating women; History of other malignancies except cured basal cell carcinoma of the skin and carcinoma in-situ of uterine cervix; serious respiratory, cardiovascular or kidney disease; prior VEGFR inhibitor treatment.

Treatment Methods

Following disease progression after first-line treatment, patients were offered apatinib at a dose of 500 mg once daily until disease progression or intolerable. One dose reduction (to 250 mg) due to drug-related toxicity was allowed. Dose-limiting toxicity was defined as possibly or definitely drug-related grades

3-4 toxic responses. Apatinib was provided by Jiangsu Hengrui Medicine Co., Ltd and was administered orally. One treatment cycle was 28 days long.

Evaluation of efficacy and safety

Clinical and radiologic evaluations were conducted at baseline and at 1 month; thereafter every 2 months or whenever clinically indicated until disease progression. At 1 month and 6 months following apatinib administration, tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Definitions of the four categories of tumor response are listed in Table 1. Progression-free survival (PFS) was defined as the length of time from enrollment (1st apatinib administration) to investigator-assessed disease progression or death from any cause, whichever occurred first. Objective response rate (ORR) was defined as the percentage of patients with an objective response among all cases and calculated as the CR rate plus the PR rate. Disease control rate (DCR) was defined as the percentage of patients with CR or PR, or SD. Treatment efficacy was evaluated by CT or MRI. AEs and severe adverse events (SAE) were classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), v4.03. Apatinib-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.0. A schematic illustration of the study overview is shown in **Figure 1**.

Category	Definition
Complete response (CR)	Complete disappearance of all target lesions
Partial response (PR)	≥30 % decrease in tumor diameter from baseline
Stable disease (SD)	Small changes that do not meet the above criteria
Progressive disease (PD)	>20% increase in tumor diameter from baseline

Table 1: Four response categories
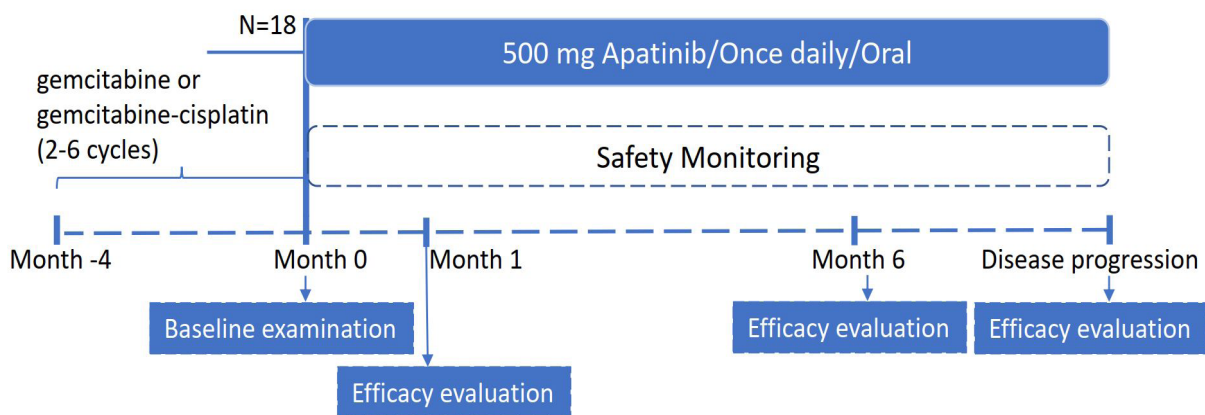
Figure 1: Study overview

Statistical Analysis

Data analysis was performed with Graph Pad Prism Software Version 7.04 (Graph Pad Software, San Diego, CA, USA). Kaplan–Meier survival curves were used for PFS estimation. P-values < 0.05 were considered statistically significant.

Results

Patient characteristic

Before data cutoff, 18 patients with advanced BTC received their first dose of apatinib, including 12 patients (67%) with cholangiocarcinoma and 6 patients (33%) with gallbladder carcinoma. The metastatic site included liver, retroperitoneal node, lungs, and supraclavicular lymph node. All pathological results were confirmed at Qinhuangdao Forth Hospital, China. Patient characteristics at baseline are summarized in Table 2. Within 4 months before apatinib administration, all patients had received gemcitabine as a single agent or in combination with cisplatin for 2-6 cycles (only 3 patients who were over 60 years old received gemcitabine monotherapy; all other patients received the combined regimen) and, unfortunately, the disease progressed. The patients' median age was 55 years and males counted for 78%. Eight cases (44%) were post-surgery recurrence, while the other 10 (56%) were initially diagnosed, patients. All patients started apatinib at a dosage of 500 mg; in 6 patients (33%), the apatinib dose was reduced to 250 mg daily within the first10 days due to intolerable toxicity.

Evaluation of efficacy

After 1 month of treatment with apatinib, all patients who had received at least one dose of apatinib were analyzed for tumor response, including 2 withdrawal cases. Although no patient was rated as having CR, PR occurred in 6 patients, including in 2 with gallbladder carcinoma and 4 with cholangiocarcinoma. Seven patients experienced SD of whom 2 had gallbladder carcinoma and the other 5 cholangiocarcinomas. In addition, 3 patients suffered from PD, including 2 with gallbladder carcinoma and 1 with cholangiocarcinoma. The ORR was 33%, while the DCR was 72%. At 6-month follow-up, except for another 4 discontinuations, there were 8 patients remained SD (2 with gallbladder carcinoma, 6 with cholangiocarcinoma) and 4 patients (2 with gallbladder carcinoma, 2 with cholangiocarcinoma) had

PD, which resulted in a DCR of 44%. All patients were followed up until progression of the disease. All 18 patients, including 6discontinued cases, were counted for Kaplan-Meier analysis for PFS. The median PFS was 8 months for the whole population; it was 2.5 months for gallbladder carcinoma and 8 months for cholangiocarcinoma. Kaplan-Meier curve for PFS presenting the whole cohort is depicted in Figure 2A; Figure 2B compares the curves for gallbladder carcinoma and cholangiocarcinoma.

Image data for a 65-year-old male patient are shown in Figure 3A, 3B and 3C. He was diagnosed with cholangiocarcinoma and underwent complete resection in August 2013. Unfortunately, pulmonary metastasis occurred in Aril 2016 and he had received gemcitabine-cisplatin for 2 cycles before PD was diagnosed. He started to take 500 mg of apatinib orally per day from 12 June 2016. One month later, the size of the targeted lesion had decreased from approximately 6.5*4 cm to 4.6*3.5 cm. Thereafter, the tumor was further shrunk to approximately 3.2*2 cm at 2.5 months after treatment. Dose reduction was needed due to fatigue and hypertension. Following symptomatic treatment, symptoms were palliated. The disease progressed in Feb 2017, indicating a PFS of 8 months.

Evaluation of safety and toxicity Fatigue, hypertension, and proteinuria were the most frequently encountered toxicities in this study. Up to 13 of the patients (72%) suffered from fatigue, 11 patients (61%) developed hypertension, while 8 patients (44%) had proteinuria. Most AE cases were grade 1 or 2, see Table 3. Four patients required apatinib discontinuation due to grade 3 AEs, including 2 hypertension cases, 1 diarrhea and 1 hand-foot syndrome case; and all recovered after drug withdrawal. Two patients gave up cancer treatment due to grade 3 hypertension and fatigue and for personal reasons. No bleeding cases, grade 4 AEs, or drug-related deaths occurred.

For hypertension, patients were given valsartan at a dose of 80 mg twice daily or 80 mg of valsartan in combination with 5 mg of levamlodipine once daily. Most diarrhea cases did not involve abdominal pain, and loperamide was prescribed. For grade 1 & 2 hand-foot syndrome, lanolin cream was applied locally to alleviate pain, ulcer, and desquamation. Loperamide had a better effect on diarrhea than montmorillonite and Bifidobacterium.

Characteristics		Number of patients
Sex	**Male**	14
	Female	4
Age (years)	**Median**	55
	40-50	4
	50-60	9
	60-70	5
Metastatic site		
From cholangiocarcino ma	Liver	2
	Retroperitoneal node	5
	Lungs	3
	Supraclavicular lymph node	2
From gall-bladder cancer	**Liver**	2
	Gallbladder (locally advanced)	4
Initial treatment/ recurrence		
Initial treatment		10
Post-surgery Recurrence		8
Gemcitabine (first-line medicine) therapy		
Monotherapy		3
Gemcitabine-cisplatin		15
Initial dosage of apatinib (mg)		
500		12
250 (dosage reduced from 500 within the first 10 days)		6

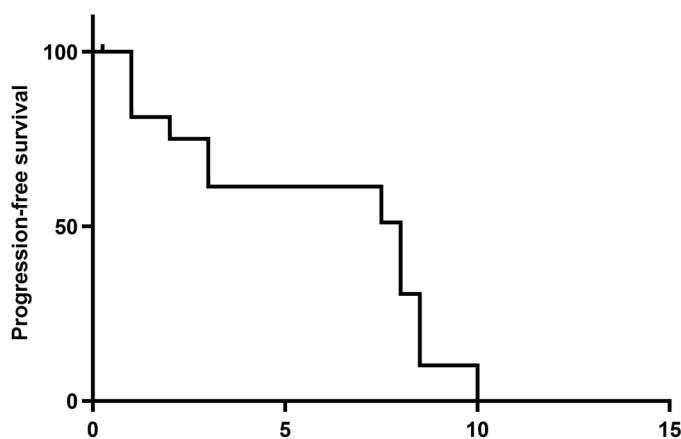Table 2: Patient characteristics

Figure 2A: Overall progression-free survival (PFS) for patients with advanced biliary tract cancer treated with apatinib monotherapy as a second-line regimen. The median PFS was 8 months.
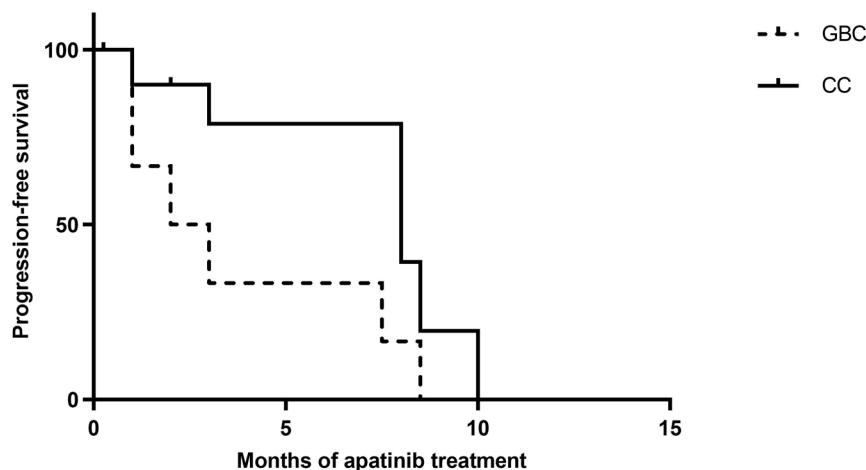
Figure 2B: Progression-free survival (PFS) for patients with advanced cholangiocarcinoma (CC) and gallbladder carcinoma (GBC) treated with apatinib monotherapy as a second-line regimen. The median PFS in GBC group was 2.5 months and in CC group was 8 months, p=0.052
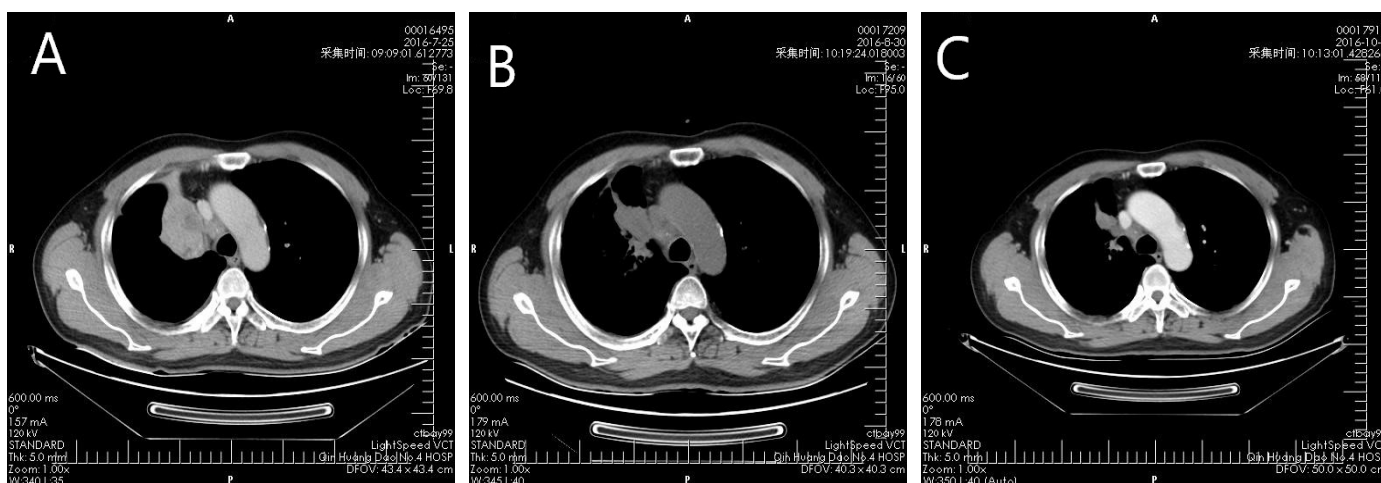

Figure 3: Images of a 65-year-old male patient with cholangiocarcinoma after treatment with apatinib monotherapy. Contrast-enhanced CT at baseline (A) showed an approximately 6.5*4 cm cholangiocarcinoma. CT images at 1 month (B) and 2.5 months (C) after baseline showed the tumor shrunk to 4.6*3.5 cm and 3.2*2 cm, respectively.

Adverse events	Total, n%	Grade	
		G1-G2	G3
Hypertension	11 (61%)	7	4
Diarrhea	6 (33%)	5	1
Hand-foot syndrome	5 (28%)	4	1
Proteinuria	8 (44%)	7	1
Fatigue	13 (72%)	11	2
Liver dysfunction	2 (11%)	2	-
Anemia	2 (11%)	3	-
Neutropenia	2 (11%)	2	-
Thrombocytopenia	1(6%)	1	-

Table 3: Treatment-related adverse events.

Discussion

To our knowledge, this is the first study evaluating the efficacy and safety profile of apatinib as a second-line treatment in patients with advanced BTC. The median PFS was 8 months, while the 1-month ORR was 33% and DCR was 72%, the 6-month DCR was 44%. Furthermore, apatinib had a manageable toxicity profile.

Even though surgery is potentially curative, BTC has a high recurrence rate due to its aggressive nature. The vast majority of patients therefore also received systemic chemotherapy, where the current standard therapy is gemcitabine plus cisplatin [33]. The strategy for second-line treatment after failure of first-line chemotherapy in advanced BTC remains unclear as research in this field is insufficient. Twenty-five studies were evaluated in a systematic review, including 14 phases II clinical trials, 9 retrospective studies, and 2 case reports to determine the level of evidence for the use of second-line chemotherapy in patients with BTC; a mean PFS of 3.2 was observed [34]. Furthermore, a multicenter survey of 174 patients reported a median PFS of 3.0 months and a pooled analysis of 499 patients reported a median PFS of 3.1 months after second-line chemotherapy [35]. These results indicate a limited value of chemotherapy as a second-line treatment for advanced BTC. Efforts devoted to establishing second-line therapies are therefore pivotal to determine what constitutes successful management of advanced BTC.

Apatinib is a highly selective VEGFR-2 inhibitor. An in vitro study demonstrated that VEGF/VEGFR-2 was significantly over-expressed in the intrahepatic tissue of patients with cholangiocarcinoma and apatinib suppressed the anti-apoptotic process induced by VEGF signaling and promoted cell death in intrahepatic cholangiocarcinoma cell lines (RBE and SSP25) [36]. Meanwhile, in cholangiocarcinoma cell lines (QBC939 and TFK-1), apatinib was reported to inhibit VEGF-mediated cell migration and invasion by inhibiting VEGF- 2/RAF/MEK/ERK and P13K/AKT pathways [37]. Furthermore, in a case report, apatinib was used for a 23-year-old female with advanced unresectable intrahepatic cholangiocarcinoma as second-line treatment and a PFS of 6 months were observed [38].

To further study the response to apatinib, we retrospectively analyzed the safety and efficacy data of apatinib as a second-line regimen in patients with advanced BTC, revealing a median PFS of 8 months. In the present study, the outcome of apatinib monotherapy was associated with a longer median PFS time than what has previously been reported with chemotherapy [34, 35, 39], and our findings mirror the above-mentioned result from the case report [38]. This indicates that targeted therapy, especially with agents targeting VEGF pathway, might constitute a breakthrough in establishing a second-line treatment for advanced BTC.

Though both cholangiocarcinoma and gallbladder carcinoma fall under BTC, they may be in fact distinct diseases with differences in prognosis and patterns of recurrence [40].

Additionally, immunohistochemical analysis for BTC samples has revealed the tumor somatic variants and genomic heterogeneity between the two diseases [41]. In this study, cholangiocarcinoma seemed more responsive to apatinib monotherapy than gallbladder carcinoma, as the median PFS was 8 months in patients with cholangiocarcinoma compared with 2.5 months in patients with gallbladder carcinoma. The arbitrary significance level was not fully reached (P=0.0502). Still, cholangiocarcinoma showed a clear tendency towards a better survival outcome than gallbladder carcinoma, which deserves more in-depth studies to determine the underlying mechanism.

Previous studies with VEGF inhibitors across a variety of tumor types established a set of AEs attributed to antiangiogenic therapy, the most well-documented of which were hypertension, arterial thromboembolic events, proteinuria, bowel perforation, reversible posterior leukoencephalopathy syndrome wound complications, and hemorrhage [13,42]. In the present study, the majority of treatment-related AEs were fatigue, hypertension, proteinuria, diarrhea, and hand-foot syndrome, which is consistent with prior findings. We found somewhat higher rates of grade 3 AEs (9 cases) than previous studies and it's with other tumor types as there are few studies on BTC, which might due to the compromised general status of advanced BTC patients. However, most of these AEs could be relieved by dose interruptions and reductions, followed by careful symptomatic treatment. No bleedingcases or treatment-related death occurred.

A multitude of trials reported using lapatinib at a dose level of 750 mg or 850 mg. However, we found that BTC patient was intolerant to such high dosages in practice. In the present study, a dose of 500 mg was used based on the patient's age, body weight, and general status; in 6 patients, the dose was reduced to 250 mg daily due to intolerability. Several limitations of the present study should be acknowledged. First, the sample size was relatively small and the drop-out rate was high. Six out of 18 patients withdrew from the study due to AEs, which could bias the efficacy results. Second, no overall survival (OS) data were obtained. Even though PFS was widely accepted as an adequate surrogate and even more meaningful than OS [43, 44], OS

remains important for efficacy prediction. Another limitation is the absence of a control group to control for confounding from external factors. Therefore, large, well-designed, randomized controlled trials are needed to confirm these results.

In conclusion, the results of the present study reinforce the hypothesis that apatinib may have the potential to act as an effective second-line agent in the treatment of advanced BTC with a manageable safety profile. However, further randomized controlled studies are needed to verify the results obtained from this single-center, retrospective study.

Author Contribution

Conception and design: Yue Zhao

Collection and assembly of data: Yue Zhao, Jianmei Li, and Chunyuan Tian

Data analysis and interpretation: Wenqian Gu and Yue Zhao

Manuscript writing: Wenqian Gu, Yue Zhao, Jianmei Li, and Chunyuan Tian

Final approval of manuscript: Yue Zhao, Wenqian Gu, Jianmei Li, and Chunyuan Tian

Ethical Statement

Approval for this study was obtained from the ethics committee of Qinhuangdao Forth Hospital, China; all procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the principles of the Declaration of Helsinki.

Disclosure

The authors declare that they have no conflicts of interest in this work.

Acknowledgments

Data Availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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