Apatinib for patients with metastatic biliary tract carcinoma refractory to standard chemotherapy: results from an investigator-initiated, open-label, single-arm, exploratory phase II study

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Abstract

Background: There is no standard therapy for metastatic biliary tract carcinoma (BTC) refractory to first-line chemotherapy. Apatinib, a VEGFR2 tyrosine kynase inhibitor, showed an activity against BTC xenografts in preclinical models. We conducted an exploratory study to evaluate the efficacy and safety of apatinib in patients with metastatic BTC.

Methods: This is a single-arm phase II study [ClinicalTrials.gov identifier: NCT03427242]. Eligible patients were aged 18 years or older; histologically confirmed metastatic BTC; refractory or intolerance to at least one chemotherapeutic regimen; no prior use of anti-angiogenic targeted drugs; Eastern Cooperative Oncology Group performance status of 0–2. Patients received oral apatinib 500 mg each day continuously until unacceptable toxicity or tumor progression. The primary endpoint was progress free survival (PFS). The secondary endpoint was overall survival (OS), objective response rate (ORR) and treatment safety.

Results: A total of 22 patients were recruited. All of them received apatinib medication. The median age was 63 (44–75) years old. Twenty patients received efficacy evaluation after treatment. The objective response rate (ORR) and disease control rate (DCR) were 15.0% and 60.0%, respectively. The median PFS was 2.73 months [95% confidence interval (CI): 1.74–3.72 months], with 6 months PFS rate of 27.3% (95% CI: 8.7–45.9%). The median OS was 4.81 months (95% CI: 3.16–10.9 months), with 12 months OS rate of 36.4% (95% CI: 16.2–56.6%). Nine out of 22 patients (40.9%) had grade 3/4 adverse events. The most common grade 3/4 adverse events were hand-foot skin syndrome [three (13.6%) patients] and hypertension [two (9.1%) patients]. No treatment-related death occurred.

Conclusions: For patients with metastatic BTC, apatinib showed an anti-tumor activity with acceptable safety, which deserves the further clinical trial.

This trial was prospectively registered on ClinicalTrials.gov [NCT03427242]. Date of first patient enrollment: 26 January 2018. Date of registration (date of first posted): 9 February 2018.

Keywords: apatinib, biliary tract carcinoma, metastasis, refractory, targeted therapy

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Introduction

Biliary tract carcinomas (BTCs) are a heterogenous group of malignant tumors originating from the epithelial cells of the biliary system, consisting of two major parts: gallbladder cancer and cholangiocarcinoma, with distinct pathological and

epidemiological characteristics. Cholangiocarcinoma can further be divided into intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) according to the site of occurrence.[1] Approximately more than 60% of patients with BTCs are detected at an advanced stage at the time of diagnosis and develop with recurrence despite radical surgery.[2]

The median overall survival (OS) for advanced BTCs receiving optimal supportive care is only 2.5–4.5 months, and chemotherapy has been widely used in advanced patients to extend survival time and improve quality of life.[3] Gemcitabine combined with cisplatin (GP) has been established as the standard first-line treatment regimen for advanced biliary carcinoma, based on the positive results of the phase III ABC-02 trial[4] and a phase II Japanese trial.[5] Compared with gemcitabine alone, median progression-free survival (PFS) of patients with the GP regimen increased from 5 to 8 months and the median overall survival (OS) increased from 8.1 to 11.7 months in the combination chemotherapy group ($p < 0.001$). In addition, promising results of gemcitabine plus S-1 doublet from the phase III FUGA-BT trial and gemcitabine plus oxaliplatin doublet from the GERCOR study also provide alternatives for patients with BTCs in the first-line setting.[6,7] Still, rapid disease progression is inevitable.

Unfortunately, only less than one third of patients could receive later-line therapy after disease progression of first-line treatment according to the performance status and organ function.[8] Currently, there is no established second-line treatment for patients with advanced BTCs who have progressed on standard first-line chemotherapy. Due to the low incidence and strong heterogeneity, reports of clinical research of advanced BTCs after failure of first-line treatment were still limited. The second-line treatment remains largely controversial in the oncological community.[9] Recently, primary results of the phase III ABC-06 trial had provided evidence for the use of second-line chemotherapy after progression of primary treatment, in which the FOLFOX regimen plus active symptom control (ASC) improved OS after progression on cisplatin plus gemcitabine compared with ASC alone, but chemotherapy led to more grade 3/4 adverse events (AEs).[10] Meanwhile, the ABC-06 trial could not prove that the FOLFOX regimen in the second-line setting was superior to fluorouracil alone, as

indicated by a multicenter retrospective analysis in 525 patients with advanced BTCs.[11]

With the advent of the 'precision medicine era', targeted therapy has become a new method of drug therapy after chemotherapy in cancer management, as well as in BTCs. However, clinical studies based on the genomic information were still limited to ICC and primarily focused on isocitrate dehydrogenase (IDH) and fibroblast growth factor receptor (FGFR) targeted therapies.[12–14]

Apatinib is an oral small molecule tyrosine kinase inhibitor (TKI) that highly selectively binds and inhibits vascular endothelial growth factor receptor (VEGFR)-2 from China. It can inhibit tumor angiogenesis by inhibiting VEGFR tyrosine kinase activity, blocking the signal transduction induced by VEGF binding to its receptor, so as to achieve the purpose of tumor treatment.[15] Based on favorable results from phase III clinical trials, apatinib has currently been approved for the third-line and subsequent-line treatment of advanced gastric or gastroesophageal junction adenocarcinoma and for the second-line treatment of advanced hepatocellular carcinoma (HCC) in China.[16,17] Besides, apatinib has displayed promising efficacy and safety in clinical studies of various advanced solid tumors, including breast cancer, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), colorectal cancer, soft tissue sarcoma, and so on.[18,19] However, to date, no clinical trials of apatinib treatment in patients with advanced BTCs have been reported. The preclinical study on BTC has shown that apatinib can inhibit the anti-apoptotic effect of intrahepatic cholangiocarcinoma cells and delay the tumor formation in mouse grafts.[20]

Therefore, this phase II clinical trial was conducted to evaluate the clinical benefit of apatinib monotherapy in patients with metastatic BTCs, after failure of the first-line or later-line therapy, and to evaluate fully the efficacy and safety of the study regimen. Patients were enrolled in this prospective study, with the primary endpoint of PFS. The OS, objective overall rate (ORR), disease control rate (DCR) and safety were the secondary endpoints.

Patients and methods

Patients
This is a single-center, investigator-initiated, single-arm, open-label, exploratory phase II clinical

trial [ClinicalTrials.gov identifier: NCT03427 242], which has been approved by the Institutional Review Board (IRB) of Fudan University Shanghai Cancer Center (Shanghai, China) (the approval number of the IRB was 1709176-9-1710). Between January 2018 and July 2020, eligible patients with metastatic BTC who had failed previous chemotherapy at Fudan University Shanghai Cancer Center were enrolled in the trial to received oral apatinib treatment, with prospective collection of patients' clinical information. All patients have provided written informed consent for the trial before enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of China.

Inclusion and exclusion criteria

The eligibility criteria of the study were as follows: (a) aged 18 years or older; (b) histologically confirmed unresectable locally advanced BTCs or metastatic BTCs; (c) prior refractory or intolerance to at least one chemotherapeutic regimens (including gemcitabine); (d) at least one measurable lesion as defined by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1); (e) the Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2; (f) acceptable hematological, hepatic, and renal function within 7 days from screening: blood absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L; hemoglobin ≥ 9.0 g/dl, the blood platelet count $\geq 80 \times 10^9$ /L, total bilirubin $<1.5 \times$ upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $<2.5 \times$ ULN ($<5 \times$ ULN for patients with live metastasis), serum creatinine $\leq 1 \times$ ULN, endogenous creatinine clearance rate >50 ml/min.

Patients could not have any of the following conditions: (a) existing uncontrolled hypertension or diabetes; patients with $>$grade 1 coronary heart disease, cardiac arrhythmias or cardiac dysfunction; (b) symptomatic brain or meningeal metastasis; (c) uncontrolled pleural or peritoneal effusion; (d) abnormal coagulation function or those receiving thrombolytics or anticoagulants; (e) with tendency of gastrointestinal hemorrhage, including active peptive ulcer with fecal occult blood no less than 2+, hematemesis or melena within 3 months; (f) urine test with 2+ protein or higher within 7 days before enrollment; (g) unresolved $\geq$grade 2 AEs (classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03) from former treatment.

Therapeutic administration

All eligibly enrolled patients received oral apatinib (apatinib mesylate tablets, 250 mg; Jiangsu HengRui Medicine Co. Ltd., Lianyungang, Jiangsu, China) at an initial dose of 500 mg, 30 minutes after dinner once every day. Daily oral apatinib should be taken at the same time of the day if possible. Treatment continued until disease progression, unacceptable AEs, or withdrawal of consent. The period of every administration and observation cycle was 28 days.

If the patients experienced grade 3/4 AEs, it was recommended to suspend the apatinib medication temporarily until symptoms resolved or relieved to $\leq$grade 2. Then, the oral dose of apatinib could be reduced to 250 mg per day or continued with the dose modification until reaching a minimum dose of 250 mg every other day. In the case of administration interruption for toxicity, a maximum of 28 days was allowed for recovery of toxicities before withdrawal from the study. If AEs of patients were judged unrelated to apatinib, treatment with apatinib monotherapy could be maintained at the original dose.

The entire medical procedures of diagnosis, treatment and follow-up from each subject were fully collected. After treatment, the blood pressure of every patient was monitored three times a week. Patients were examined by laboratory every 2 weeks. In these assessments, patients were monitored for hematology, serum chemistry and urinalysis. In addition, their ECOG performance status, vital signs (including blood pressure, heart rate, respiratory rate and temperature) and electrocardiogram were also measured and followed up by investigators every cycle. The blood tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were also tested at baseline and every cycle. All the AEs were recorded and assessed according to the NCI CTCAE version 4.03.

Response evaluation

Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan was performed at baseline and every two cycles (8 weeks, consistent with baseline) after treatment initiation. The objective response of patients was

clinically evaluated by investigators from the department of radiology, according to the RECIST version 1.1 criteria.[21] Complete remission (CR) and partial remission (PR) were identified as objective response. Response judged as CR, PR, or SD was defined as disease control. In this study, the time frame for response assessment by CT/MRI was 8 weeks, and the response recorded for each patient was the best of all evaluation results during the treatment.

Statistical analysis

This trial was a single-arm study and in the sample size calculation we assumed the historical control as the control arm. The calculation was processed with PASS (Power Analysis and Sample Size) 15.0 software (NCSS LLC, Kaysville, Utah, USA), based on the log-rank test to assess PFS with apatinib *versus* historic control. The one-sided significance level was assumed at 0.1 and the power at 80% with 1:1 randomization. To demonstrate an improvement of median PFS from 1.5 months in the historic control arm to the anticipated 3.0 months for patients treated with apatinib with an accrual time of 36 months and follow-up time of 12 months, the subject number needed for the apatinib arm was 46. After considering the potential proportion dropping out of treatment arm of 20%, the anticipated sample size in the treatment arm was 55 subjects. Thus, a total of 55 patients were planned for enrollment.

The analysis of endpoints was prospectively designed and preplanned. All quantitative data were shown in the terms of medians. The primary endpoint was PFS, which was measured from the time of enrolment to the day of tumor progression or death from any cause. Patients with no evidence of progression were censored for PFS at the date of the last follow-up. Secondary endpoints were OS (defined as the period from the time of enrolment to death from any cause), ORR (defined as the proportion of patients achieving objective response), DCR (defined as the proportion of patients achieving disease control), and the AEs of all enrolled patients. Patients who were still alive at the time of the last follow-up were censored for OS on that date. Survival curves were estimated using the Kaplan–Meier method. The survival data from all enrolled patients were calculated on the basis of an intention-to-treat (ITT) analysis. Safety data were analyzed in patients who received at least one

dose of apatinib. The median follow-up time was calculated as the median of all enrolled subjects.[22] All subgroup analysis was unplanned and designed before patient recruitment.

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated by the Cox proportional hazard model. The *p* values were calculated from the log-rank test with a one-sided α of 10% and power of 80%. The univaiate analysis of PFS and OS within different subgroups was performed using the log-rank test. The variates with a *p* value ≤0.05 would be further tested in a multivariate model by regression to identify independent prognostic factors.

All statistical analyses were performed with the Statistical Package for the Social Sciences, version 20.0 (SPSS, Inc., Chicago, IL, USA). The *p* value <0.05 was defined as statistically significance.

Results

Study population

From 26 January 2018 to 1 July 2020, a total of 22 patients with metastatic BTC were enrolled in this study. In this study, the whole enrollment time was planned to be 3 years, but due to the slow speed of enrollment, only 22 patients were enrolled within the 2.5 years (from January 2018 to July 2020) after the beginning of enrollment, which had not yet reached the expected enrollment number. Therefore, we discontinued subsequent enrollments and here these 22 patients were reported in the final analysis.

The baseline clinical characteristics of all 22 patients are shown in Table 1.

All 22 patients were administered with at least one dose of apatinib, and 20 received response evaluation (Figure 1). At the cut-off date (4 February 2021) for analysis of efficacy and safety, two patients were still on medication of apatinib and six patients were still alive, with a median follow-up time of 5.25 months (range 0.97–24.93 months). Among the 20 patients who discontinued the study regimen, two patients stopped the treatment permanently due to intolerable toxicity (one for grade 3 vomiting and one for grade 3 pneumonitis), and the other 18 patients stopped this regimen due to disease progression. Patients received medication of apatinib

for a median of 2.68 months (range 0.37–21.10 months). Twenty-one patients received an initial dose of 500 mg for apatinib treatment, and one patient started apatinib treatment at a reduced dose of 250 mg due to a history of interstitial lung disease.

Clinical response

A total of two patients dropped out early in the study due to toxicity before any clinical evaluation was made. In the assessable population ($N=20$), three of 20 patients achieved the clinical objective response (three with PR and none with CR), thus the ORR was 15.0% (95% CI: 0–30.0%). Nine patients (45.0%) had SD and eight (40.0%) had PD, thus the DCR was 60.0% (95% CI: 40–80.0%). The ORR was 10.0% (1/10) in patients with ICC, 50.0% (1/2) in patients with ECC and 12.5% (1/8) in patients with gallbladder cancer. The objective response and DCRs in selected subgroups are shown in Table 2.

The primary endpoint

The PFS events happened in 20 patients. In the ITT population, the median PFS assessed by investigators was 2.73 months (95% CI: 1.74 months–3.72 months) [Figure 2(a)]. The estimated PFS rate at 3 months was 50.0% (95% CI: 29.3–71.0%). The estimated PFS rate at 6 months was 27.3% (95% CI: 8.7–45.9%). The median PFS of subgroups by different clinical characteristics was retrospectively analyzed by univariate Cox regression.

Despite this exploratory trial having a very small number patients within each subgroup, the Kaplan–Meier plot displayed that the median PFS of patients with response of PR was dramatically better than that of patients with SD and PD (mPFS: 15.83 *versus* 4.43 *versus* 2.03 months, respectively; $p=0.000$) [Figure 2(b)].

Also, the baseline blood level of CA19-9 (>1000 U/ml; ULN to 1000 U/ml; normal) was significantly correlated with PFS (HR=3.087; 95% CI: 1.374–6.934; $p=0.006$). The higher level CA19-9 before treatment indicated a much poorer PFS (mPFS of normal *versus* ULN to 1000 U/ml *versus* >1000 U/ml: 17.03 *versus* 4.43 *versus* 2.03 months, respectively; $p=0.007$) [Figure 2(c)].

Table 1. Baseline characteristics of patients ($N=22$).

Characteristics	Number of patients	Percentage (%)
Age (years)		
Median	63	
Range	44–75	
Sex		
Male	12	54.5
Female	10	45.5
ECOG performance status		
0	4	18.2
1	16	72.7
2	2	9.1
Baseline level of CA19-9 (U/ml)		
Highly elevated (≥1000)	8	36.4
Mildly elevated (ULN 1000)	11	50.0
Normal	3	13.6
Primary site		
Intrahepatic bile duct	11	50.0
Extrahepatic bile duct	2	9.1
Gallbladder	9	40.9
Resection of primary lesion		
Yes	15	68.2
No	7	31.8
Number of metastatic organs		
1	5	22.7
≥2	17	77.3
Involved metastases		
Liver	10	45.5
Lung	8	36.4
Lymph node	12	54.5
Peritoneum	9	40.9
Abdominal wall	2	9.1
Bone	2	9.1
Lines of previous chemotherapy		
1	14	63.6
≥2	8	36.4

ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.
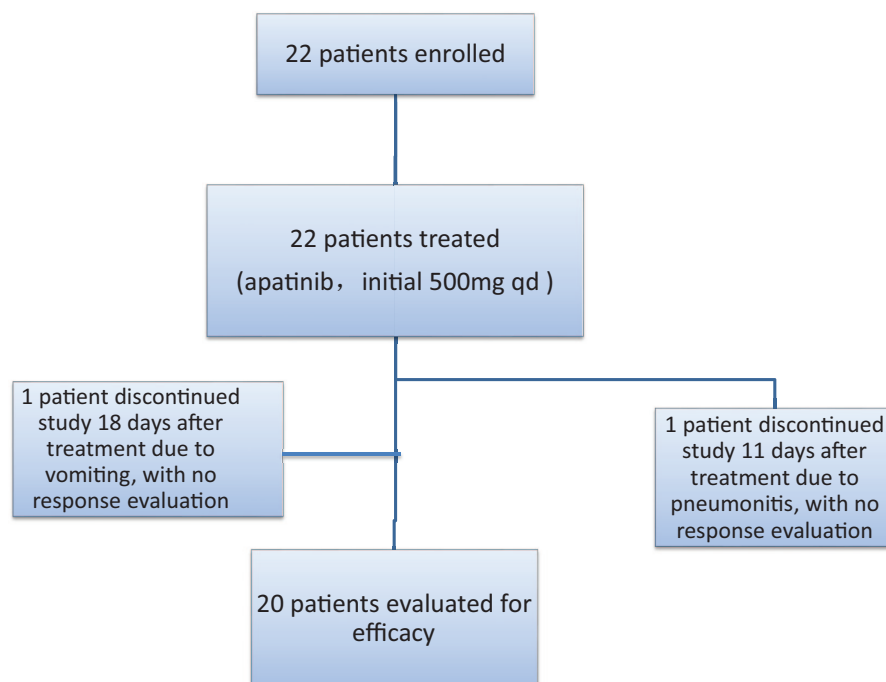
Figure 1. The trial flowchart.

However, the sex, age, primary site, resection of primary tumor, ECOG performance status, lines of previous treatment, number of metastatic organs, lung metastasis or not, liver metastasis or not, were found to have no obvious influence on PFS.

Overall survival

After a median follow-up time of 5.25 months, 16 patients had died. The median OS of the ITT population was 4.81 months (95% CI: 1.84–7.90) [Figure 3(a)]. The 6 months OS rate was 45.5% (95% CI: 24.7–66.3%), and the 12 months OS rate was 36.4% (95% CI: 16.2–56.6%). The results from the univariate log-rank test for different clinical characteristics were highly consistent with those of PFS. Both the clinical response of PD, SD or PR (HR = 4.325; 95%CI: 1.562–11.974; $p = 0.005$) and baseline level of CA19-9 of more than 1000 U/ml, ULN to 1000 U/ml or normal (HR = 7.710; 95%CI: 2.434–24.426; $p = 0.001$) were prognostic indices of OS. Patients with better clinical response obviously had a longer OS ($p = 0.002$) [Figure 3(b)]. Also clearly, a lower level of baseline CA19-9 indicated a distinctly better OS ($p = 0.000$) [Figure 3(c)].

Adverse events

The AEs related to treatment are shown in Tables 3. The most common AEs of any grade were hypertension (19 patients, 86.4%), fatigue (16 patients, 72.7%), palmar-plantar erythrodysesthesia syndrome [also called hand-foot skin reaction (HFSR), 11 patients, 50.0%], anorexia (10 patients, 45.5%), proteinuria (10 patients, 45.5%). A total of 40.9% patients (9/22) experienced grade 3–4 AEs. All the detailed grade 3 or 4 toxicities for apatinib treatment in this trial were palmar-plantar erythrodysesthesia syndrome (three patients, 13.6%), hypertension (two patients, 9.1%), platelet count decreased (also called thrombocytopenia, one patient, 4.5%), proteinuria (one patient, 4.5%), nausea and vomiting (one patient, 4.5%) and pneumonitis (one patient, 4.5%).

Dose reductions due to AEs occurred in 10 (54.5%) patients, of whom eight patients were asked to reduce the dose due to grade 3 AEs, two patients voluntarily reduced the dose due to grade 2 HFSR. Seven (31.8%) patients had dose interruptions due to AEs.

The only severe adverse event (SAE) during the study treatment period was grade 4 pneumonitis

in one patient, after receiving apatinib for 11 days at an initial dose of 500 mg. The patient was admitted to the intensive care unit (ICU) for treatment of a severe pulmonary infection and recovered after 2 weeks, discontinuing apatinib therapy permanently. Another patient stopped the treatment and quit the trial due to intolerable grade 3 nausea and vomiting after apatinib administration for 18 days even after a dose reduction to 250 mg per day. Thus, a total of two patients stopped the treatment of study regimen due to drug-related toxicity.

The AEs of apatinib were consistent with the known safety profile and no unexpected toxicities appeared. No treatment-related deaths (grade 5 AE) occurred. All deaths in the trial were caused by tumor progression.

In a *post-hoc* analysis, the patients with treatment-related HFSR ($n = 11$, 50%) had a longer OS than those without this type of toxicity (median OS 12.83 months *versus* 4.23 months; HR = 0.344; 95% CI: 0.119–0.997; log-rank $p = 0.041$) [Figure 3(d)]. The PFS of those with HFSR had a tendency to be longer than that of those without, but the difference was not statistically significant (median PFS 3.53 months *versus* 2.70 months; HR = 0.511; 95% CI: 0.191–1.368; $p = 0.173$) [Figure 2(d)]. In the further analysis, with the cuff-off point set at a median OS of 4.81 months, enrolled patients were divided into those with OS <4.81 months ($n = 10$) and with OS ⩾4.81 months ($n = 12$). For patients with OS <4.81 months, HFSR no longer had the prognostic impact on OS ($p = 0.593$). For patients with OS ⩾4.81 months, HFSR was not the prognostic factor for OS, neither ($p = 0.904$), indicating that HFSR might not be the actual prognostic factors for survival.

Discussion

The aim of this exploratory phase II clinical study was to evaluate the efficacy and safety of apatinib, an oral anti-VEGFR TKI, in patients with metastatic BTC who were refractory to at least one line of gemcitabine-based chemotherapy. To our knowledge, this is the first reported prospective trial evaluating the monotherapy of apatinib in later lines of treatment in patients with metastatic BTC. The PFS was set as the primary endpoint of the expeditionary study, for the reason that a relatively small sample size was required, considering the low incidence and poor prognosis of

Table 2. Objective response rates to apatinib treatment in seleted subgroups.

Response assessment ($N = 20$)		
All patients	**Number**	**Rate (%)**
Complete response	0	0
Partial response	3	15.0
Stable disease	9	45.0
Progressive disease	8	40.0
Overall response	3	15.0
Disease control	12	60.0
Patients with ICC ($n = 10$)		
Overall response	1	10.0
Disease control	8	80.0
Patients with ECC ($n = 2$)		
Overall response	1	50.0
Disease control	1	50.0
Patients with gallbladder cancer ($n = 8$)		
Overall response	1	12.5
Disease control	3	37.5
Patients with liver metastasis ($n = 9$)		
Overall response	2	22.2
Disease control	6	66.7
Patients with lung metastasis ($n = 6$)		
Overall response	1	16.7
Disease control	3	50.0
Patients with lymph node metastasis ($n = 10$)		
Overall response	1	10.0
Disease control	5	50.0

ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

BTC, in which only a quarter of patients would be eligible for second-line therapy.[8] Within 2.5 years (January 2018 to July 2020), a total of 22 eligible patients from Fudan University Shanghai Cancer Center were enrolled and received apatinib treatment. The results displayed that mPFS for ITT analysis was 2.73 months, with a 3-month PFS rate of 50.0%, and 6-month PFS rate of
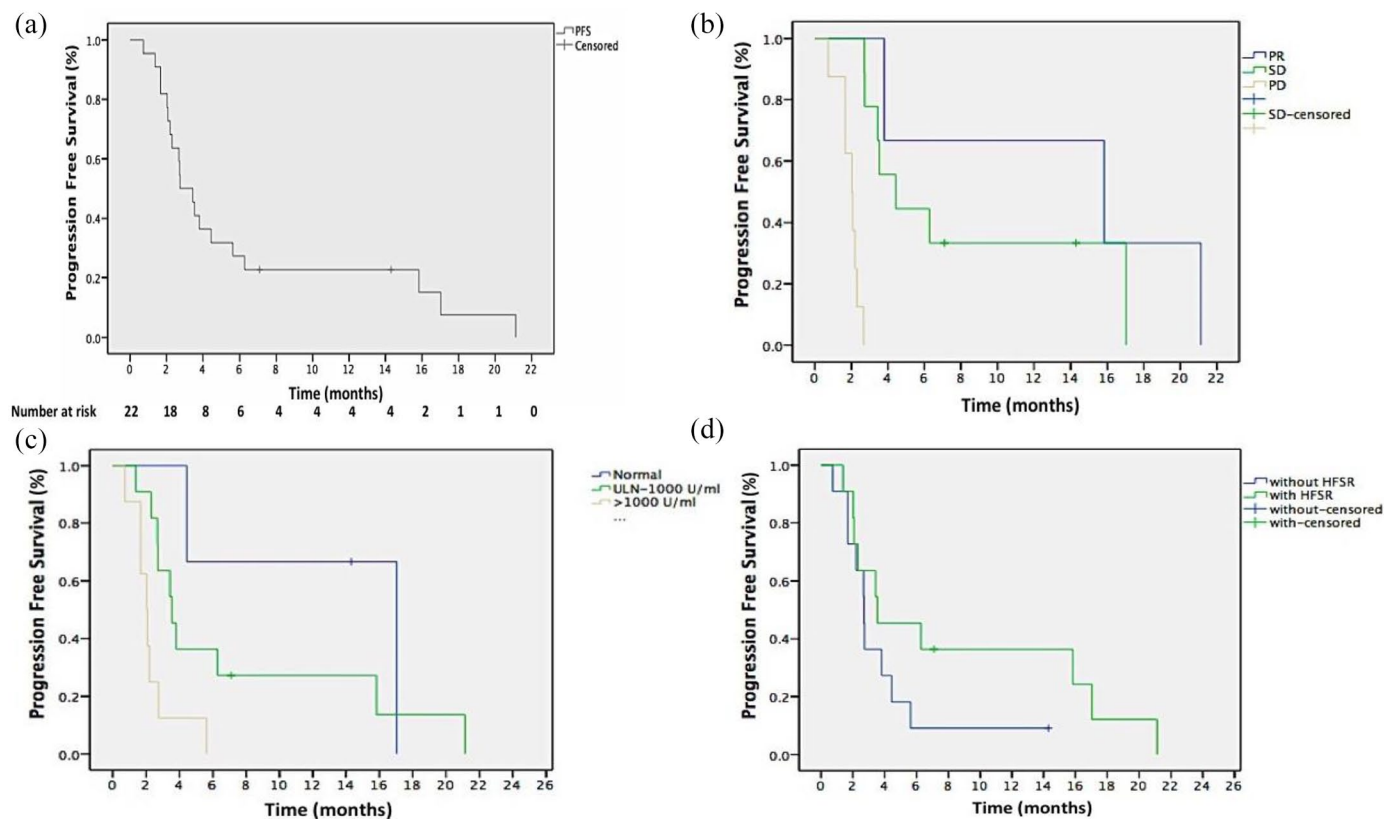
Figure 2. Kaplan–Meier curves of investigator-assessed progression-free survival (PFS) (a). The investigator-assessed PFS of patients with PR, SD and PD (b). The investigator-assessed PFS of patients with different baseline levels of CA19-9 (c). The PFS of patients with or without treatment-related hand-foot skin reaction (HFSR) (d).

27.3%, indicating a promising antitumor activity for apatnib, in line with our expectations. The safety data also showed a good tolerance of oral apatinib in metastatic BTC.

Actually, in the majority of biliary tract cancers, which are rare but prone to recurrence and metastasis despite tumor resection, palliative or systemic therapies might be the only beneficial therapeutic options. However, only a few prospective clinical trials have shown the survival benefits of chemotherapy in patients with advanced biliary tract cancer in the earlier time.[3,23] The doublet regimen of GP or gemcitabine plus S-1 (GS)[4,6] have been established as standard treatment of first-line chemotherapy. Disappointingly, most of patients with metastatic BTC deteriorate rapidly after first-line treatment failure. In the ABC-02 trial, only 15% of patients received second-line systemic therapy.[4] The possibility of following treatment largely depended on their functional performance status and organ function.[8] For a long time, no second-line therapy has been established in BTC. A systematic review

including 761 patients had analyzed the role of second-line therapy in advanced BTC, showing an average PFS of 3 months and OS of 7 months, with an overall ORR of 8%.[8] Encouragingly, the ABC-06 trial might be the only randomized controlled phase III trial which successfully showed a significant survival benefit of the FOLFOX regimen plus active symptom control as the second-line treatment for advanced BTC by far.[10] Results showed that patients who received second-line chemotherapy had a higher 6-month OS rate of 51% and 12-month OS rate of 36%, compared with those without chemotherapy, at a cost of significantly more grade 3 or more AEs. However, that trial only included patients with a good performance status (ECOG 0–1), which could only represent a part of the patient population with metastatic BTC who were refractory to standard therapy in the real world.

Tremendous advances in targeted and immunotherapy in other types of advanced tumor also raised the hope of survival benefit made by these therapies in metastatic BTC. A genome analysis
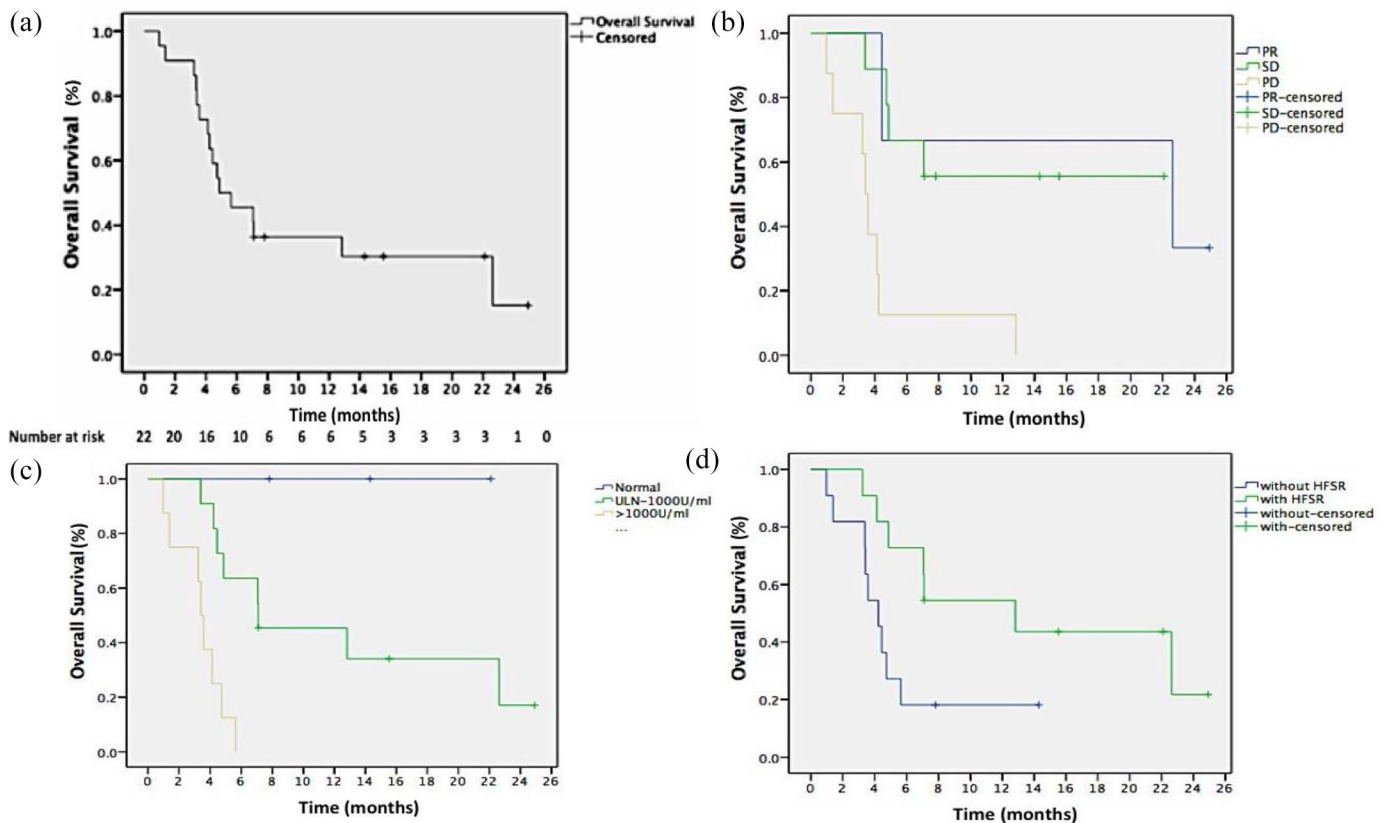
Figure 3. Kaplan–Meier curves of overall survival (OS) of the ITT population (a). The investigator-assessed OS of patients with PR, SD and PD (b). Kaplan–Meier curves of investigator-assessed OS of patients with different baseline levels of CA19-9 (c). The OS of patients with or without treatment-related hand-foot skin reaction (HFSR) (d).

of 489 tissue samples of BTC revealed the large genetic heterogeneity of tumor gene alteration profile, based on different primary lesions (intrahepatic, extrahepatic or gallbladder) and driving factors.[24] In initial clinical explorations, the targeted therapy with several other small molecular TKIs had been tested in an unselected population in the setting of second-line therapy of advanced BTC, including sunitinib,[25] sorafenib,[26] bortezomib,[27] everolimus,[28] erlotinib,[29] cediranib[30] and cabozantinib.[31] In these studies, the ORR for TKI monotherapy differed from 2–12%, with the mPFS ranging from 1.7 months to 3.2 months and mOS from 4.2 months to 7.7 months. Recently, positively encouraging results could be seen in patients with identified alteration of gene targets, mostly in tumors harboring FGFR2 gene fusion (mainly in ICC), HER2 amplification or mutation (mainly in ECC and gallbladder cancer) and IDH (mainly in ICC).[13,32,33] Positive results from these target treatments were gradually changing the clinical practice. However, only a small part (less than 20%) of patients with these specific gene mutations could be the suitable population.

The treatment of this single arm trial was monotherapy of apatinib, a novel small molecule VEGFR-2 TKI which suppresses the tumor by inhibiting tumor angiogenesis. Apatinib was firstly approved in China in 2014, based on the benefits on OS and PFS with an acceptable safety profile in patients with advanced gastric cancer refractory to at least two lines of therapy.[16] It was also approved for second-line treatment of patients with advanced HCC at the end of 2020 in China.[17] For advanced BTC, no efficacy or safety data of apatinib in any line of treatment had been prospectively reported. Our results in this trial showed that the ORR for apatinib monotherapy was 15% and the DCR of apatinib reached 60%, indicating a good anti-tumor activity. The response rate was similar to that of other anti-angiogenesis TKIs tested in advanced BTC, and was also not inferior to that (ORR 8%) of the FOLFOX regimen in the ABC-06 trial. In the

Table 3. The treatment-related adverse events in study period.

AEs	Apatinib treatment (n = 22)		
	Grade 1–2	Grade 3	Grade 4
	n (%)	*n* (%)	*n* (%)
Hematological			
White blood cell decreased	3 (13.6)	0	0
Neutrophil count decreased	3 (13.6)	0	0
Platelet count decreased	6 (27.3)	1 (4.5)	0
Anemia	5 (22.7)	0	0
Non-hematological			
Hypertension	17 (77.3)	2 (9.1)	0
Proteinuria	9 (40.9)	1 (4.5)	0
Anal hemorrhage	2 (9.1)	0	0
Epistaxis	4 (18.2)	0	0
Nausea/vomiting	3 (13.6)	1 (4.5)	0
Diarrhea	7 (31.8)	0	0
Oral mucositis	4 (18.2)	0	0
Palmar-plantar erythrodysesthesia syndrome	8 (36.4)	3 (13.6)	0
Anorexia	10 (45.5)	0	0
Fatigue	16 (72.7)	0	0
Pneumonitis	1 (4.5)	0	1 (4.5)
Blood bilirubin increased	3 (13.6)	0	0
AST increased	4 (18.2)	0	0
ALT increased	6 (27.3)	0	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
The safety population includes all enrolled patients who received at least one dose of apatinib (n = 22).
No treatment-related deaths (grade 5 AE) occurred.

recent reports from two single-arm phase II trials, regorafenib, a multi-kinase inhibitor which targeted VEGFR 1–3 and other targets, was also evaluated in patients with chemotherapy-refractory advanced BTC. Sun *et al.*[34] reported an ORR of 11% and a DCR of 55%, while Kim *et al.*[35] reported a DCR of 62.5%. In the REACHIN trial, a placebo-controlled phase II trial to demonstrate the efficacy of regorafenib in BTC, the ORR of the regorafeninib arm was 0, and the DCR was 74% in the regoragenib group and 34% with placebo (*p* = 0.002).[36]

Survival results of our study showed that the mPFS was 2.7 months and mOS of 4.8 months, which was modest. The estimated PFS rate at 3 months and 6 months was 50% and 27.3%, respectively. The estimated OS rate at 6 months and 12 months was 45.5% and 36.4%, respectively. As for the REACHIN trial, in the regorafenib arm the mPFS was 3.0 months and PFS at 6 months was 21%, compared with mPFS of 1.5 months in the placebo group (HR = 0.49; 95% CI: 0.29e–0.81; *p* = 0.004). Besides, the mOS in the regorafenib arm was 5.3 months and

survival at 12 months was 30%, compared with mOS of 5.1 months in the placebo arm ($p = 0.28$).[36] The data from our trial were also consistent with former published trials in the similar setting of second or later line treatment.

In our trial with a limited sample size, response to apitinib treatment and the baseline level of CA19-9 was significantly correlated with PFS and OS. Patients with a lower CA19-9 concentration and a better response to apatinib might have a longer PFS and OS. A reported multi-center study had showed that patients with advanced biliary tract cancer who had a better baseline performance status, a lower CA19-9 concentration and tumor surgery would have a better prognosis with second-line therapy, compared with those without these characteristics.[37] However, it had been mentioned that the number of patients included in our trial is so small that none of these prognostic analyses could be conclusive.

In this study, the AEs of apatinib monotherapy with an initial dose of 500 mg were generally mild and well tolerated. The grade 3/4 hematological AE was rare (one patient with grade 3 thrombocytopenia, 4.5%). The profile of toxicity was within expectations and similar to what had been reported in previous phase III trials.[16] Hypertension was the most common AE occurring in patients with apatinib treatment, with an incidence rate at any grade of (86.3%). The vast majority of treatment-related hypertension was grade 1–2, and no grade 4 hypertension happened. Half of the patients suffered from treatment-related HFSR of any grade and 72.7% of them were in grade 1–2, consistent with the results of former apatinib trials. Most of the AEs were manageable and well controlled. Hemorrhage had been reported as the AE of particular concern for apatinib, as the VEGFR inhibitor may increase the risk of bleeding. In our study, no grade 3/4 hemorrhage-related AEs appeared. Only one SAE happened and no treatment-related death occurred during the study period.

It had to be mentioned that our study had some limitations. This study was a non-randomized trial with a single arm of a small sample size. The enrolled patients were only from Fudan University Shanghai Cancer Center and the entire speed of enrollment of this trial was relatively slow, due to the low number of eligible patients.

In conclusion, this is the first exploratory phase II trial to show that apatinib has a favorable anti-tumor activity with good safety in patients with metastatic BTC who are refractory to standard therapy. Larger trials of apatinib treatment on BTC are urgently needed in the future.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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