Clinical Case Report

Medicine®

OPEN

Apatinib for treating advanced intrahepatic cholangiocarcinoma after failed chemotherapy

A case report and literature review

Li-Ye Wang, MM, Shuai Gong, MD, Li-Ping Gao, MM, Li-Xia Hou, MM, Wei He, MD*

Abstract

Rationale: Intrahepatic cholangiocarcinoma (ICC) originates from the secondary branch of the bile duct and the intrahepatic bile duct epithelial cells, and is a rare pathological type of primary liver cancer. Recently, apatinib has been successfully used for a variety of malignancies.

Patient concerns: A 23-year-old female was noted with intermittent right upper abdominal distension, abdominal pain, and vomiting after eating for more than 1 month. The enhanced CT scan revealed multiple intrahepatic lesions, portal vein and right branch tumor emboli were present.

Diagnosis: Combined with the patient's medical history and pathology and immunohistochemistry, the diagnosis was confirmed as locally advanced unresectable ICC (cT4N1M1, Stage IVB).

Interventions: The disease progressed after six cycles of gemcitabine plus capecitabine chemotherapy. She received oral apatinib treatment since September 30, 2017. Due to related adverse reactions, the patient could not tolerate the treatment, and the subsequent reduction therapy was given.

Outcomes: On April 11, 2018, the review of CT evaluation suggested that the disease was progressed. Hence, in this patient, apatinib as second-line treatment for advanced ICC showed a progression-free survival with 6 months.

Lessons: Apatinib as second-line treatment for advanced ICC is effective, and the adverse effects are tolerable. However, the efficacy and safety of apatinib in the treatment of ICC need to be further confirmed by large sample of prospective randomized controlled trials.

Abbreviations: BTC = biliary tract cancer, EGFR = epidermal growth factor receptor, ICC = intrahepatic cholangiocarcinoma, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial remission, RPLS = reversible posterior leukoencephalopathy syndrome, RR = response rate, SD = stabilization of disease, TTP = time to progression, VEGF = vascular endothelial growth factor.

Keywords: anti-angiogenesis, apatinib, biliary tract cancer targeted therapy, intrahepatic cholangiocarcinoma

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from the secondary branches far from the intrahepatic bile duct epithelial cells. It is a rare pathological type of primary liver cancer. The proportion of primary liver cancer is less than 5%. The incidence of the disease is high in patients aged 30 to 50 years, and its incidence rate has increased in recent years.[1] Surgical resection is currently the only means of radical treatment, but because of its hidden features, the early diagnosis rate is low. Most of the patients are in the middle-late stage at the time of treatment and lose the opportunity for radical surgery. However, because patients with advanced ICC are prone to recurrence, metastases, and poor prognosis, therapeutic regimens are limited with low sensitivity to radiochemotherapy. The median survival time is reported to be 3 to 6 months.[2]

No standard treatment guideline exists for advanced biliary tract cancer (BTC), 5-fluorouracil or gemcitabine is used as the first-line treatment regimen. Its survival time is slightly longer, and no standard second-line treatment regimen is available. Clinic studies of targeted agents have been attempted to improve the outcomes of the disease. Those primary targeted agents are monoclonal antibodies and tyrosine kinase inhibitors against epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).[3]

Apatinib is an anti-angiogenesis drug developed independently in China. Apatinib was approved and accepted by the China State Food and Drug Administration in October 2014 as a subsequent-line treatment for advanced or metastatic chemo-refractory gastric cancer.[4] It is a small-molecule tyrosine kinase inhibitor

Editor: N/A.

Ethical approval: Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Institutional review board statement: The case report was reviewed and approved by the Institutional Review Board of First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

Data sharing statement: No additional data are available.

The authors have no funding and no conflicts of interest to disclose.

Department of Oncology, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China.

* Correspondence: Wei He, Department of Oncology, First Affiliated Hospital of Zhengzhou University, No. 1, Jianshe East Road, Zhengzhou 450052, Henan Province, China (e-mail: hewei726@126.com).

Medicine (2018) 97:49(e13372)

Received: 8 August 2018 / Accepted: 31 October 2018

http://dx.doi.org/10.1097/MD.0000000000013372

targeting VEGF receptor 2 (VEGFR-2).[5] VEGFR-2 is crucial in anti-apoptosis mediated by VEGF. VEGF inhibits apoptosis through the VEGFR-2/PI3K/Akt/mTOR pathway. Apatinib treatment increases cell apoptosis by inhibiting the signal transduction of VEGF. The first indications for apatinib are third-line therapy in patients with advanced gastric cancer or gastroesophageal adenocarcinoma.[6] However, apatinib has been successfully used for a variety of malignancies such as advanced non-small cell lung cancer, pancreatic cancer, ovarian cancer, breast cancer, hepatocellular carcinoma, colon cancer, and even angiosarcoma.[7–10] However, its therapeutic effect on ICC has not been reported. This study reported the efficacy of apatinib as a second-line treatment for metastatic ICC after the failure of the first-line treatment of gemcitabine plus capecitabine chemotherapy.

2. Case report

The patient was a 23-year-old female. On May 2, 2017, she visited the hospital complaining of intermittent right upper abdominal distension, abdominal pain, and vomiting after eating for more than 1 month. The physical examination showed no positive signs in the skin and mucous membrane without yellow dye staining. She had a history of chronic hepatitis B for 8 years without antiviral treatment and no family history of cancer. The related examinations improved after admission; hepatitis B virus DNA quantification was 5.53E + 0.3 IU/mL, serum carbohydrate antigen 19–9 (CA19–9) level was 58.34 U/mL, and liver function showed grade II liver function impairment. The thoracic and total abdominal enhanced CT scan revealed multiple intrahepatic occupancies with portal vein and right branch thrombosis and the largest intrahepatic mass is 19.21 mm, multiple hypodense hepatic nodules and their rims were enhanced in the arterial phase (Fig. 1A–C). Small nodules in the right middle lobe and enlarged lymph nodes were detected behind the retroperitoneum (Fig. 1D). Subsequently, she underwent a liver biopsy, and the mass pathology showed adenocarcinoma with clinical considerations of primary biliary origin or metastasis (Fig. 2). Based on these examinations, the patient was diagnosed with locally advanced unresectable ICC (cT4N1M1, Stage IVB).

Owing to multiple intrahepatic occupancies and enlarged lymph nodes detected behind the retroperitoneum, this patient cannot choose surgery. According to the National Comprehensive Cancer Network Clinical Practice guidelines, the patient was

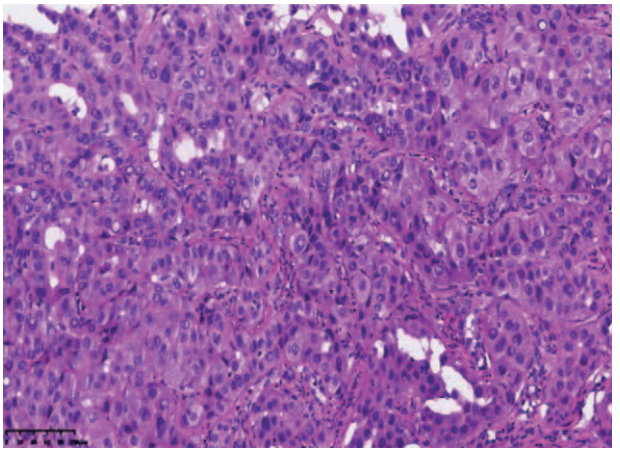

Figure 2. Hematoxylin and eosin staining of a tumor section (× 200). The pathological diagnosis was adenocarcinoma. Consider primary biliary origin or metastasis. Immunohistochemical staining showed that CK, CK8/18, CK19, CK7, and Villin were positive, while Hep and TTF-1 were negative.

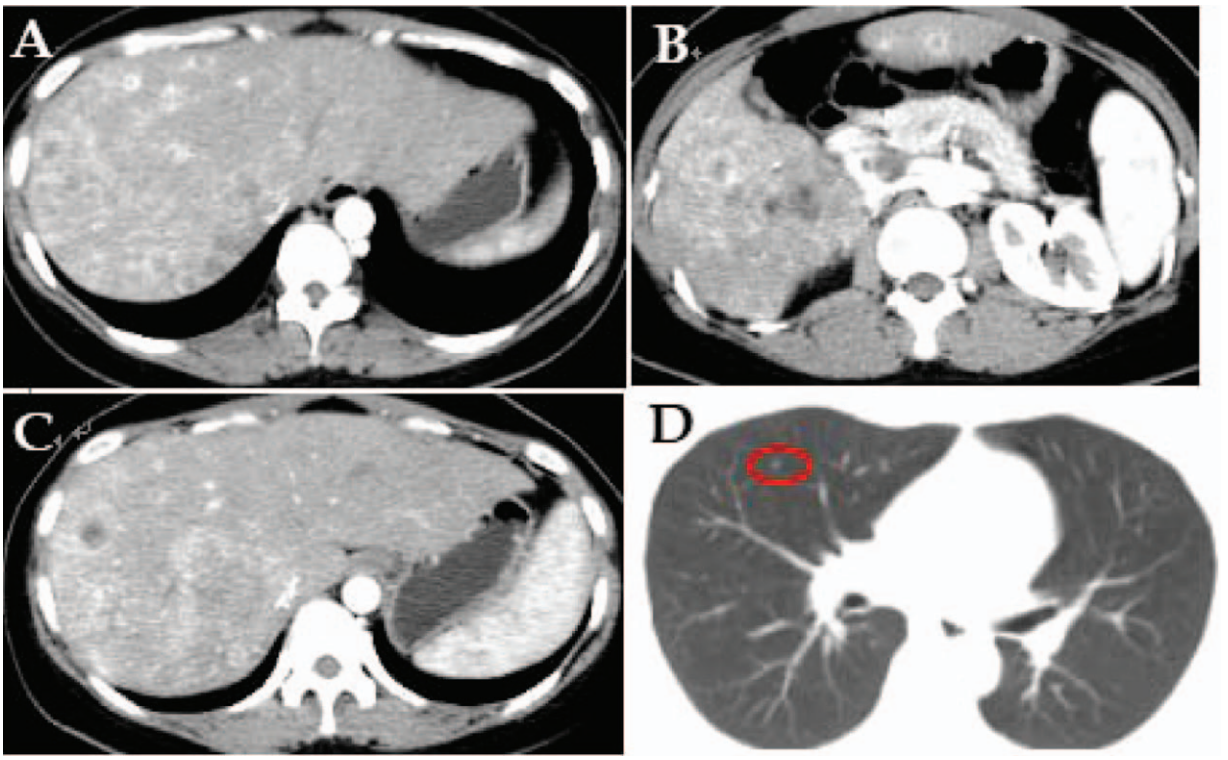

Figure 1. abdominal enhanced computed tomography (CT) showed multiple intrahepatic occupancy (A–C). Right middle lung nodules (D).

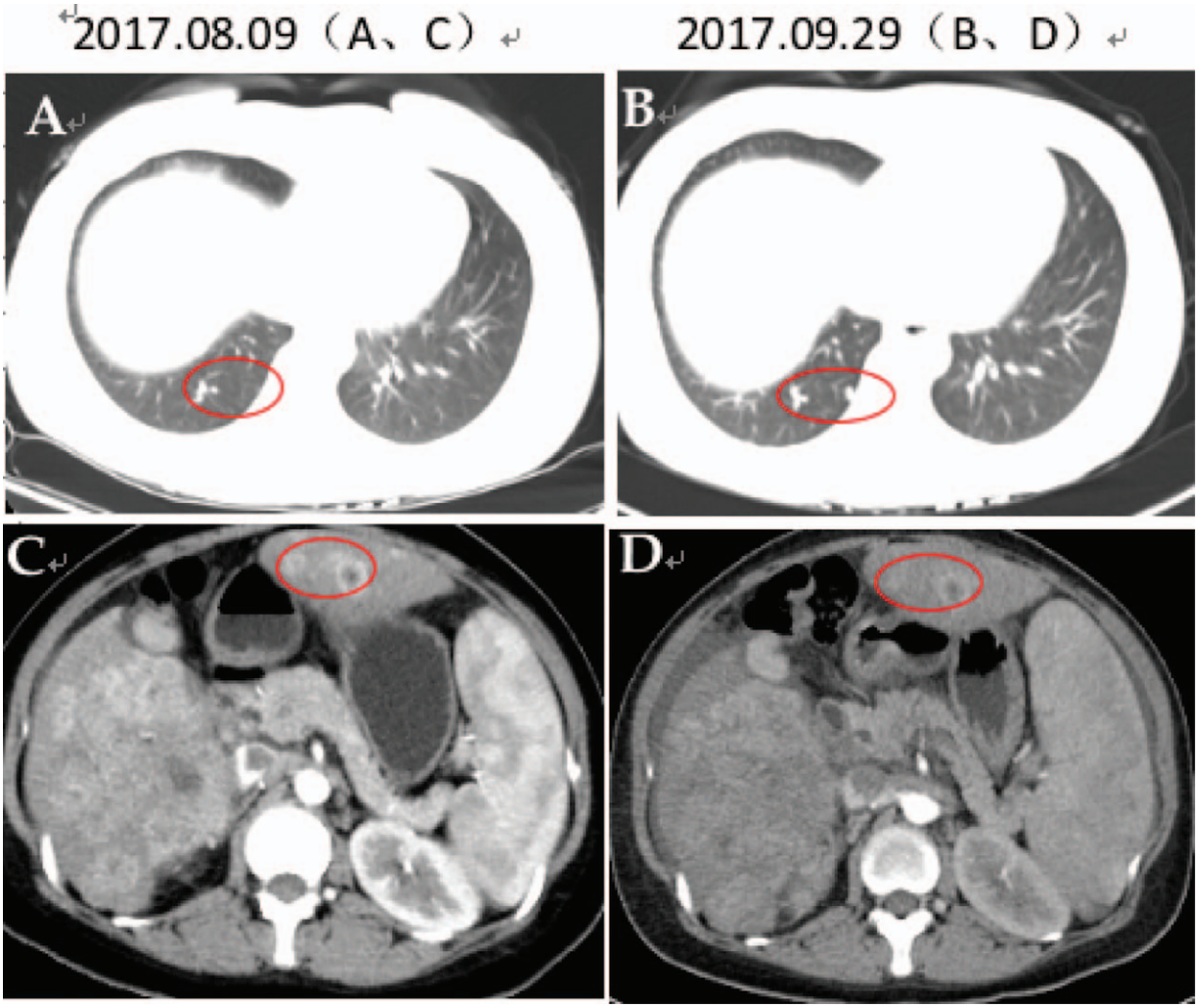

Figure 3. computed tomography (CT) showed multiple pulmonary nodules increased compared with the previous (lung window A, B and C, D). The lesions in the liver remained stable (E and F).

initially treated with a traditional chemotherapeutic regimen that consisted of six cycles of gemcitabine and capecitabine [gemcitabine (1000 mg/m^2) on days 1 and 8 intravenously and capecitabine orally (1.5 g BID) D1–14, q21D] after two cycles. The chest examination and full-abdomen enhanced CT showed that the scheme was effective. The efficacy in the second and fourth cycles of chemotherapy after enhanced CT was evaluated as stabilization of disease (SD) [based on the solid tumor efficacy evaluation criteria (Response Evaluation Criteria in Solid Tumors, RECIST 1.0)]. The patient was not treated with gemcitabine on day 8 in the sixth cycle due to the development of moderate anemia. During chemotherapy, the patient developed the primary side-effects of myelosuppression (degree 3), vomiting (grade 2), and a higher serum alanine transaminase level (grade 1) according to the Common Terminology Criteria for Adverse Events v4.0 Criteria. All side-effects were well controlled with drug treatment. After six cycles of treatment, the enhanced CT showed an increase in multiple small pulmonary nodules compared with the previous cycle (Fig. 3A and B lung window), and the efficacy was evaluated as progressive disease (PD).

Since the use of apatinib in ICC was not approved, the molecular targeted therapy in which the patient received oral apatinib (500 mg/d) began on September 30, 2017 after signed informed consent. Dizziness, blurred vision, swollen face, vomiting, anorexia, and other side-effects developed on the fifth day after discharge. Headache, chest tightness, breathing difficulties, numbness of the limbs, chills, sweating, body aches, weakness, and generalized edema developed gradually on day 10, but no hematologic toxicity was observed. The patient did not stop or reduce the dose, and the aforementioned symptoms were slightly relieved after self-administration of analgesic, antiemetic, and diuretic drugs. On the 23rd day, the patient did not take the medicine. Convulsions in limbs occurred in the morning. The patient fainted after foaming at the mouth and woke up after 2 days in the intensive care unit, and was then transferred to the oncology department for 10 days for treatment and improvement in microcirculation. She could not tolerate the side-effects and hence stopped taking apatinib on October 22, 2017. All aforementioned side-effects disappeared after discontinuing the medicine. On November 11, 2017, an abdominal enhanced CT scan revealed a decrease in liver lesions with a marked reduction in the enhancement (Fig. 4B and D) and a clear decrease in the CT value (Fig. 4C and D). As the patient was unable to tolerate the side-effects of apatinib, the amount of apatinib was reduced to 250 mg/d on November 9, 2017. After taking the medicine, facial edema, dizziness, headache, blurred vision, and other complica-

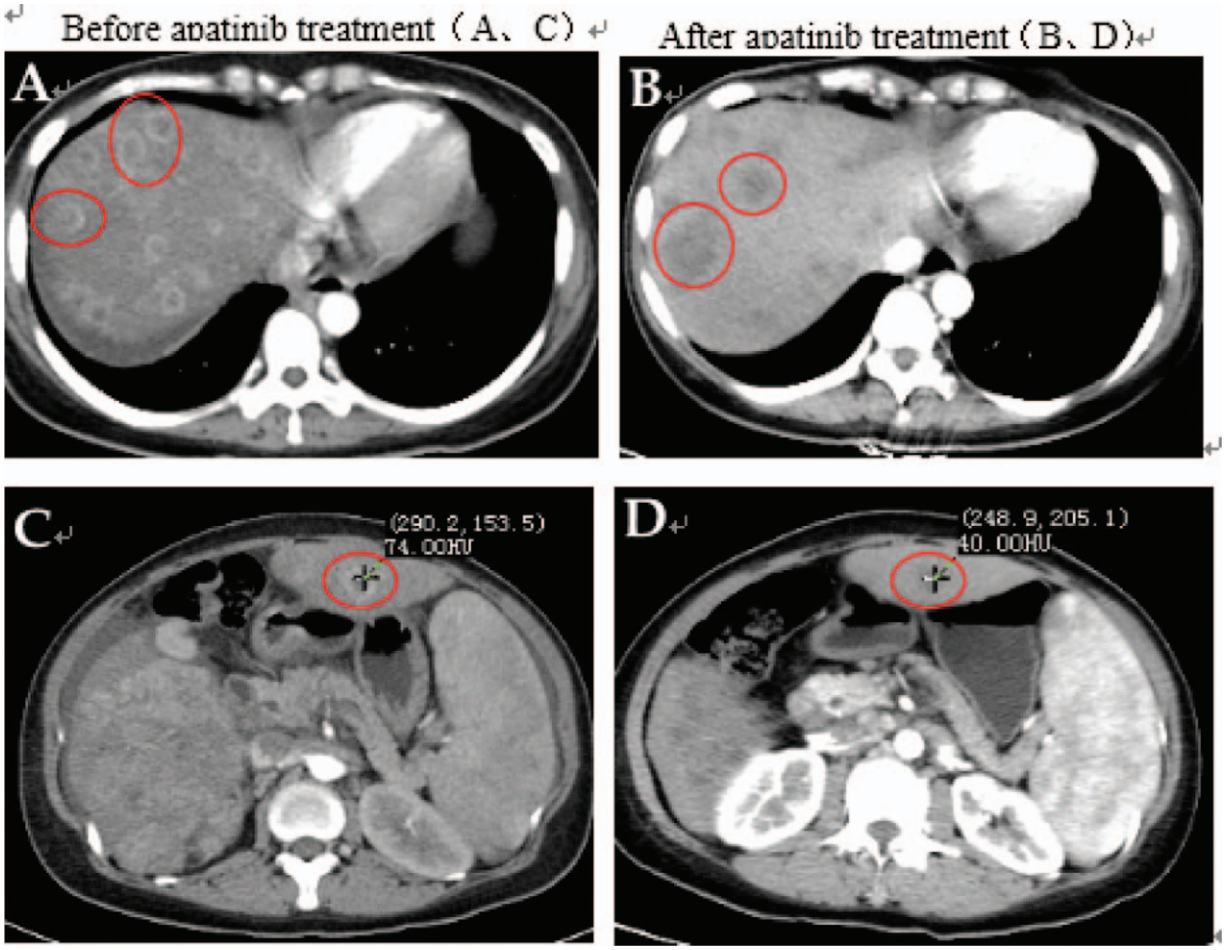

Figure 4. On November 11, 2017, an abdominal enhanced CT scan revealed a decrease in liver lesions (B and D) compared with that before (A and C), with a marked reduction in enhancement (B and D) and a clear decrease in CT value (C and D) during apatinib treatment.

tions gradually appeared on the second day. The blood pressure was 136/100 mm Hg. Hence, nifedipine sustained-release tablets were taken to control blood pressure. The patient continued to take apatinib 250 mg/d, and the self-reported tolerance was acceptable Table 1.

Due to differences in the mechanisms of action of anti-angiogenic drugs, enhanced CT was significantly or partially effective when the efficacy was evaluated as SD according to the RECIST guideline. Therefore, when evaluating the efficacy of anti-angiogenic drugs, the RECIST standard was not

Table 1

Clinical trials using targeted agents for advanced or metastatic biliary tract cancer.

Targeted drug	Mechanism	Phase	Stage	N	Arm	PFS, mo	OS, mo	ORR
Sorafenib[21]	VEGFR-2/3	II	Metastatic/relapse	46	Sorafenib	2.3	4.4	32.6%
Cediranib[22]	VEGFR-1/2/3	II	Metastatic/relapse	124	A: cediranib + gemcitabine + cisplatin	8.0 vs. 7.4	14.1 vs. 11.9	44% vs. 41%
					B: Placebo + gemcitabine + cisplatin	*P*=0.72	*P*=0.44	
Sorafenib + erlotinib[23]	VEGF + EGFR	II	Locally advanced/ metastatic	34	Sorafenib + erlotinib	2.0	6.0	6%
Cetuximab[24]	EGFR	II	Advanced biliary tract cancer	150	A: cetuximab + gemcitabine + oxaliplatin	6.1 *vs.* 5.5	11 *vs.* 11.4	24% *vs.* 23%
					B: gemcitabine + oxaliplatin			
Panitumumab[25]	EGFR + KRAS (WT)	II	Metastatic biliary tract cancer	89	A: panitumumab + gemcitabine + oxaliplatin	5.3 *vs.* 4.4	9.9 *vs.* 10.2	26.6% vs. 18.1%
					B: gemcitabine + oxaliplatin	*P= 0.27*	*P= 0.42*	
Sorafenib + gemcitabine + cisplatin[26]	VEGFR-2/3	II	Metastatic/relapse	39	Sorafenib + gemcitabine + cisplatin	6.5	14.4	10.3%
Bevacizumab + erlotinib[27]	VEGF + EGFR	II	Locally advanced/metastatic	53	Bevacizumab + erlotinib	4.4	9.9	18%

EGFR = epidermal growth factor receptor, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, VEGFR = vascular endothelial growth factor receptor.

comprehensive. Instead, the CT value became a more accurate evaluation criterion.[11] In view of this standard, the patient was evaluated as partial remission (PR) after taking apatinib.

On April 11, 2018, the patient visited the hospital reexamination of the chest, and full-abdomen enhanced CT showed multiple nodules predominantly in the lungs, mediastinal lymph node enlargement, bilateral pleural effusions, and abdominal–pelvic fluid, efficacy evaluation PD. So far, apatinib as second-line treatment for advanced ICC showed a progression-free survival (PFS) with 6 months.

3. Discussion

Cholangiocarcinomas are tumors derived from biliary epithelial cells. More than 90% are adenocarcinomas, which can be divided into ICC and extrahepatic cholangiocarcinoma due to different anatomic sites. ICC is the second most common primary hepatocellular carcinoma. The incidence of ICC has increased in the last few decades. The disease is usually associated with cirrhosis, viral hepatitis B, and hepatitis C.[12] Complete surgical resection is the only possible treatment for patients with ICC. However, only 20% to 40% of patients can undergo surgical resection when diagnosed, and the 5-year survival rate is approximately 30%. The standard first-line treatment for locally advanced or metastatic cholangiocarcinoma is gemcitabine plus capecitabine chemotherapy. The replacement regimen with tegafur (S-1), an oral fluoropyrimidine, has shown a similar response rate (RR) as that with gemcitabine. In addition, S-1 has been studied as a second-line treatment for patients with advanced cholangiocarcinoma refractory to gemcitabine.[13] New drugs or chemotherapeutic regimens are urgently required as a second-line treatment option for patients with cholangiocarcinoma.

The results of previous trials showed that the effectiveness of second-line chemotherapy was limited to advanced BTC. A Phase II study was carried out to evaluate the efficacy of gemcitabine single chemotherapy as a second-line treatment in 32 patients with BTCs who evidenced disease progression after the administration of 5-fluorouracil (5-FU)-based palliative chemotherapy. The results showed that the overall effective rate was 6.9%, and the median time to progression (TTP) and median overall survival (OS) were 1.6 months and 4.1 months, respectively.[14] Another study evaluated the feasibility of gemcitabine and cisplatin combination therapy as a second-line treatment for patients with advanced BTC refractory to gemcitabine and S-1. The results showed that the disease control rate was 70%, and the median OS and TTP were 5.9 months and 3.6 months, respectively.[15] Jean-Florian et al performed a study in 32 patients to evaluate the efficacy of FOLFIRI plus bevacizumab as a second-line treatment for metastatic ICC. The RR and disease control rates were 38.4% and 84.5%, respectively. The PFS and median OS were 8 months and 20 months, respectively.[16] A recent study explored the efficacy of Pan-mTOR inhibitor MLN0128 in the ICC of mice. A novel ICC mouse model was established via the hydrodynamic transfection of activated forms of Akt (myr-Akt) and Yap (YapS127A) protooncogenes (referred to as Akt/YapS127A). The study showed the antineoplastic potential of MLN0128, suggesting that it might be superior to gemcitabine/oxaliplatin-based chemotherapy for treating ICC, especially in tumors exhibiting an activated AKT/mTOR cascade.[17] Mitesh et al performed integrated genome-wide and whole transcriptome sequence analyses on six patients with sporadic ICC. They found that pazopanib and ponatinib showed antitumor activity in patients with FGFR 2 fusion. Rapid and robust disease regression was noted in this ERRFI1-inactivated tumor when treated with erlotinib, an EGFR kinase inhibitor.[18] Another study showed that FIG-ROS inactivation in carcinomas harboring mutant Kirsten rat sarcoma (Kras) viral oncogene homolog, and P53 mutations could potently inhibit tumor growth, thereby validating ROS as a therapeutic target in ICC.[19] A multicenter, randomized, Phase III clinical trial showed that the addition of erlotinib to gemcitabine and oxaliplatin significantly prolonged median PFS [5.9 months [95% confidence interval (CI) 4.7–7.1] for chemotherapy plus erlotinib vs. 3.0 months (1.1–4.9) for chemotherapy alone; HR 0.73, 95% CI 0.53–1.00; $P = 0.049$] in patients with cholangiocarcinoma.[20] However, some of the targeted drugs in cholangiocarcinoma did not show a significant benefit compared with standard chemotherapy.

Angiogenesis is a prerequisite and key factor in the development of cancer because it provides oxygen, growth factors, and nutrients for the tumor. It is also vital in tumor growth, invasion, and metastasis and serves the basis of tumor recurrence.[28] Tumor cells co-express VEGF and VEGFRs, which interact to support self-sustained cell growth. Among all known angiogenic factors, VEGF is a key regulator of angiogenesis. VEGF acts on endothelial cells through endothelial cell-specific receptors VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3 (Flt-4) as chemokines and mitogenic agents. The downstream effects of VEGFR-2 on vascular endothelial activation include cell proliferation, migration, permeability, and survival, which are crucial in angiogenesis. Apatinib is a novel tyrosine kinase inhibitor that inhibits many tumor-associated kinases such as VEGFR-2, RET, platelet-derived growth factor-β, and stem cell factor receptor (c-Kit). Apatinib has a highly selective competition at the ATP-binding site of VEGFR-2. It then blocks downstream signaling pathways, inhibits tumor angiogenesis, decreases tumor microvessel density, and promotes apoptosis so as to achieve the purpose of inhibiting tumor growth. Apatinib can inhibit the proliferation of cholangiocarcinoma cells in a dose and time-dependent manner by inducing apoptosis and blocking the cell cycle. Phase II and Phase III studies showed a significant improvement in OS and median PFS in the apatinib group in patients with advanced gastric or gastroesophageal junction adenocarcinoma. However, in a Phase I clinical trial involving various types of tumors such as non-small cell lung cancer, breast cancer, esophageal cancer, nasopharyngeal cancer, and hepatocellular carcinoma, the drug achieved better disease control rate and the overall disease control rate was as high as 83.8%, but data on the use of apatinib in ICC are not yet available.

This study reported first-line chemotherapy failure. The ICC has no standard second-line treatment. However, it has been successfully used for treating advanced non-small cell lung cancer, pancreatic cancer, ovarian cancer, hepatocellular carcinoma, and other malignant tumors. Therefore, it was speculated that apatinib might have potential efficacy in treating ICC by selectively inhibiting VEGFR-2. Therefore, the patient was given apatinib. The patient achieved a significant effect after 6 months of PFS. However, the adverse effects of apatinib were varied. The incidence of Grade 3/4 adverse reactions was about 2%, including hypertension, hand-foot syndrome, proteinuria, fatigue, anorexia, and elevated transaminases. Most adverse reactions could be controlled and reversed through withdrawal, reduction, and optimal supportive treatment.[29] These adverse events were commonly based on previous clinical trials, case reports, and clinical experience. Reversible posterior leukoencephalopathy syndrome (RPLS)[30] is a classification of clinical radiological diseases involving the exudation of plasma components from

capillaries in the brain and vascular edema. Symptoms of RPLS include headache, spasms, drowsiness, mental disorders, blindness, visual disturbances, neurological disorders, and mild-to-severe hypertension. When RPLS is suspected, brain images, especially non-angiographic MRI diagnosis, can be used. The medication should be discontinued in the case of abnormal findings. Also, hypertension management, anticonvulsant drug administration, and other appropriate treatments may be considered. In this study, the patient underwent a variety of adverse events, especially syncope after convulsions of the limbs, considering that the patient had symptoms similar to those of the RPLS. All adverse events were well controlled after proper treatment. Further studies are needed to determine the therapeutic dose and duration of apatinib in ICC.

4. Conclusions

Advanced ICC has a high degree of malignancy, and the single treatment of poor efficacy, and apatinib can be treated as another treatment option after ICC chemotherapy resistant. The patient in this study showed good efficacy when treated with apatinib, but poor tolerance to adverse reactions and hence received reduction treatment. Angiogenesis is vital in the occurrence and development of cholangiocarcinoma. Anti-angiogenic drugs deserve further research and experimentation. Also, large-scale prospective randomized controlled trials are required to determine the safety and efficacy of apatinib in treating ICC.

Acknowledgments

We thank our colleagues from First Affiliated Hospital of Zhengzhou University for the treatment of this case, and the patient and her family members who agreed to publication of this case

Author contributions

W.L.Y. collected the case data and wrote the paper; G.S. and H. W. treated the patient; W.L.Y., G.L.P., and H.L.X. contributed to the literature search; H.W. reviewed and revised the manuscript; all authors have read and approved the final manuscript.
Data curation: Shuai Gong, Li-Ping Gao, Li-Xia Hou.
Methodology: Wei He.
Resources: Li-Ye Wang, Shuai Gong.
Writing – original draft: Li-Ye Wang.
Writing – review & editing: Li-Ye Wang, Wei He.

References

[1] West J, Wood H, Logan RF, et al. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971–2001. Br J Cancer 2006;94:1751–8.
[2] Morise Z, Sugioka A, Tokoro T, et al. Surgery and chemotherapy for intrahepatic cholangiocarcinoma. World J Hepatol 2010;2:58–64.
[3] Guro H, Kim JW, Choi Y, et al. Multidisciplinary management of intrahepatic cholangiocarcinoma: current approaches. Surg Oncol 2017;26:146–52.
[4] Zhang H. Apatinib for molecular targeted therapy in tumor. Drug Des Dev Ther 2015;9:6075–81.
[5] Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci 2011;102:1374–80.
[6] Huang J, Fan Q, Lu P, et al. Icotinib in patients with pretreated advanced esophageal squamous cell carcinoma with EGFR overexpression or EGFR gene amplification: a single-arm, multicenter phase 2 study. J Thorac Oncol 2016;11:910–7.
[7] Xu J, Liu X, Yang S, et al. Clinical response to apatinib monotherapy in advanced non-small cell lung cancer. Asia-Pac J Clin Oncol 2018;14:264–9.
[8] Li CM, Liu ZC, Bao YT, et al. Extraordinary response of metastatic pancreatic cancer to apatinib after failed chemotherapy: a case report and literature review. World J Gastroenterol 2017;23:7478–88.
[9] Lu W, Ke H, Qianshan D, et al. Apatinib has anti-tumor effects and induces autophagy in colon cancer cells. Iran J Basic Med Sci 2017;20:990–5.
[10] Ji G, Hong L, Yang P. Successful treatment of angiosarcoma of the scalp with apatinib: a case report. Onco Targets Ther 2016;9:4989–92.
[11] Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. JAMA 2009;302:2338–44.
[12] Donato F, Gelatti U, Tagger A, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. Cancer Causes Control 2001;12:959–64.
[13] Suzuki E, Ikeda M, Okusaka T, et al. A multicenter phase II study of S-1 for gemcitabine-refractory biliary tract cancer. Cancer Chemother Pharmacol 2013;71:1141–6.
[14] Oh SY, Jeong CY, Hong SC, et al. Phase II study of second line gemcitabine single chemotherapy for biliary tract cancer patients with 5-fluorouracil refractoriness. Investig New Drugs 2011;29:1066–72.
[15] Sasaki T, Isayama H, Nakai Y, et al. Feasibility study of gemcitabine and cisplatin combination chemotherapy for patients with refractory biliary tract cancer. Investig New Drugs 2011;29:1488–93.
[16] Guion-Dusserre JF, Lorgis V, Vincent J, et al. FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. World J Gastroenterol 2015;21:2096–101.
[17] Zhang S, Song X, Cao D, et al. Pan-mTOR inhibitor MLN0128 is effective against intrahepatic cholangiocarcinoma in mice. J Hepatol 2017;67:1194–203.
[18] Borad MJ, Champion MD, Egan JB, et al. Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. PLoS Genet 2014;10:e1004135.
[19] Saborowski A, Saborowski M, Davare MA, et al. Mouse model of intrahepatic cholangiocarcinoma validates FIG-ROS as a potent fusion oncogene and therapeutic target. Proc Natl Acad Sci USA 2013;110:19513–8.
[20] Lee J, Park SH, Chang HM, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2012;13:181–8.
[21] Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients 'II trial. Br J Cancer 2010;102:68–72.
[22] Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol 2015;16:967–78.
[23] El-Khoueiry AB, Rankin C, Siegel AB, et al. S0941: a phase 2 SWOG study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. Br J Cancer 2014;110:882–7.
[24] Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol 2014;15:819–28.
[25] Leone F, Marino D, Cereda S, et al. Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type KRAS advanced biliary tract cancer: a randomized phase 2 trial (Vecti-BIL study). Cancer 2016;122:574–81.
[26] Lee JK, Capanu M, O'Reilly EM, et al. A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. Br J Cancer 2013;109:915–9.
[27] Lubner SJ, Mahoney MR, Kolesar JL, et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. J Clin Oncol 2010;28:3491–7.
[28] Hiratsuka S. Vasculogenensis, angiogenesis and special features of tumor blood vessels. Front Biosci 2011;16:1413–27.
[29] Izzedine H, Rixe O, Billemont B, et al. Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. Am J Kidney Dis 2007;50:203–18.
[30] Rajasekhar A, George TJJr. Gemcitabine-induced reversible posterior leukoencephalopathy syndrome: a case report and review of the literature. Oncol 2007;12:1332–5.