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Case Report

Apatinib treatment in extensive metastatic advanced intrahepatic cholangiocarcinoma: a case report

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Abstract: Intrahepatic cholangiocarcinoma (ICC) arising from the intrahepatic bile ducts, is an uncommon and highly fatal carcinoma with overall survival confined to several months. The first line treatment of advanced ICC is gemcitabine with platinum, which is sub-optimal for ICC patients with poor physical condition. Herein, a case of extensive metastatic advanced ICC treated with apatinib is reported. Apatinib is a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor-2. During three-month treatment with apatinib, the patient achieved stable status with abdominal distension improved and imaging results showing central cavitation in tumors, although accompanied with some adverse events and ultimately progressed to death. Apatinib is still expected to be an additional option for advanced ICC treatment.

Keywords: Intrahepatic cholangiocarcinoma, apatinib

Introduction

Intrahepatic cholangiocarcinoma (ICC, also known as intrahepatic cholangiocellular carcinoma) arising the intrahepatic bile ducts, is a relatively rare and highly lethal neoplasm with a rising incidence [1, 2]. Surgical resection is the mainstay for treatment of early ICC [3], but for advanced ICC, surgical resection is not suitable and systematic chemotherapy only presents a minimal therapeutic effect [4]. For patients with advanced ICC, gemcitabine with platinum as first line treatment has a median survival of 11.7 months [4, 5]. However, in advanced ICC patients with poor physical condition, the median survival time has been reported to be 3 to 6 months [6], necessitating an evaluation of alternative drugs. Additionally, to date no molecular targeted therapy has been effective for ICC.

Apatinib (Hengrui Pharmaceutical Co. Ltd, Shanghai, China) is a small-molecule tyrosine kinase inhibitor, and can selectively target vascular endothelial growth factor receptor-2 (VEGFR-2) to suppress tumor growth. Nevertheless, few studies have applied apatinib for ICC treatment. Herein, a case of advanced ICC is reported, demonstrating that abdominal distension and imaging results were improved even with some side effects during three-month apatinib treatment.

Case report

A 65-year-old female patient with a 4-month history of abdominal distension and pain is described in this report. She received radical mastectomy for left breast cancer 5 years ago and surgical resection of ICC mass 2 years ago, and no chemotherapy was accepted after surgery. She had occult HBV infection.

Physical examination demonstrated a mass on right upper abdominal wall. On August 1st, 2017, she underwent right abdominal wall tumor resection plus right abdominal wall defect repair. Post-operative pathology suggested right upper abdominal invasive adenocarcinoma, which was considered as the metastatic lesion of ICC based on the medical history and further immunohistochemical results. The immunohistochemical analysis showed: CK (+), Vimentin (stove +), CK7 (stove +), CK20 (-), CK19 (-), TTF-1 (-), Hep (-), AFP (-), GCDFP-15 (-), ER (-), PR (-), kitchen (+), CAM5.2 (+), PAX-8 (-), P16 (small stove +), P53 (-), Ki67 (20%+), WT-1 (-) (**Figure 1**).

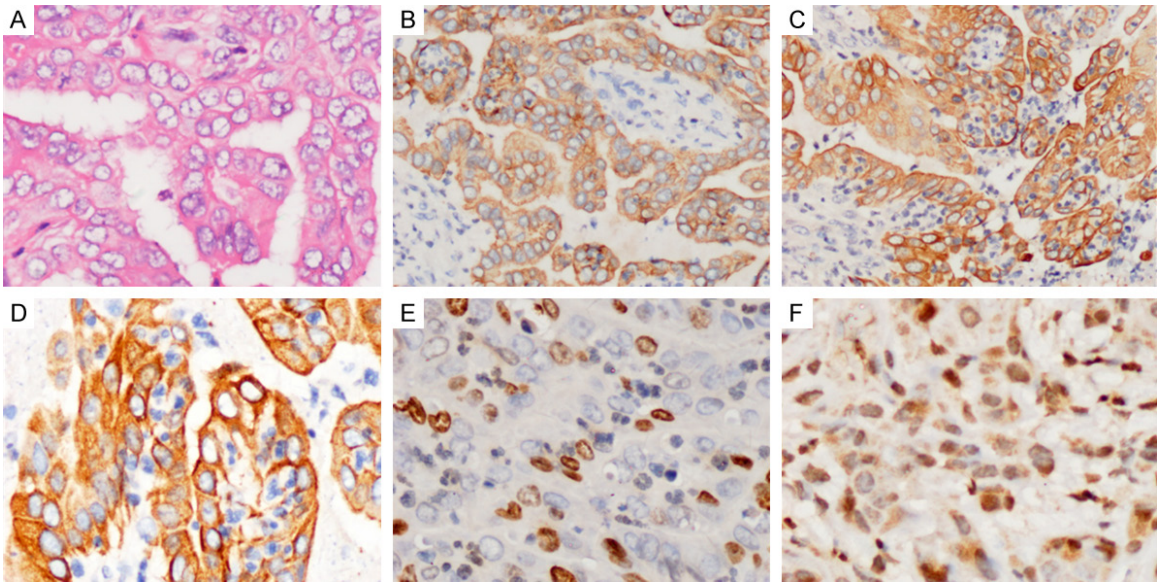

Figure 1. Pathologic evidence of intrahepatic cholangiocarcinoma. A. HE, ×40; B. CAM5.2, ×20; C. CK 7. ×20; D. CK 19, ×40; E. Ki67, ×40; F. P16, ×40. Abbreviations: CK 7, Cytokeratin 7; CK 19, Cytokeratin 19; CK 20, Cytokeratin 2).

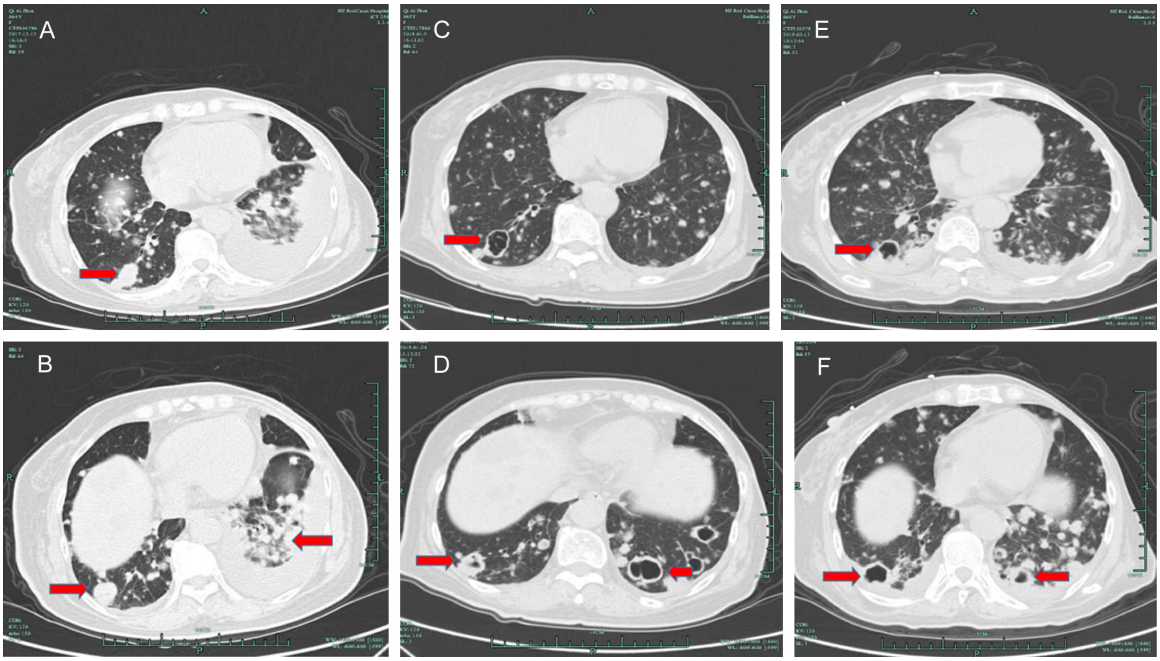

Figure 2. Chest CT (A and B, December 11, 2017) images show bilateral lung metastatic tumors and left pleural effusion in the ICC patient before apatinib treatment. Chest CT (C and D, January 24, 2018): compared with the former chest CT (A and B, December 11, 2017), multiple cavities in the bilateral lung metastases were formed and left pleural effusion was absorbed after one-month treatment of apatinib (500 mg/d). Chest CT (E and F, March 13, 2018): compared with the former chest CT (C and D, January 24, 2018), bilateral lung metastases were increased and enlarged, and bilateral pleural effusion were observed after another two-month treatment of apatinib with reduced dose (250 mg/d). Red arrow, tumor; Abbreviations: CT, computed tomography.

Chest computed tomography (CT) was performed on December 11, 2017 (**Figure 2A** and **2B**), and the result indicated bilateral lung metastatic tumors and left pleural effusion. Total abdominal enhancement CT images were collected on December 12, 2017 (**Figure 3A** and **3B**) and the result suggested multiple metastatic tumors in the liver and seroperitoneum.

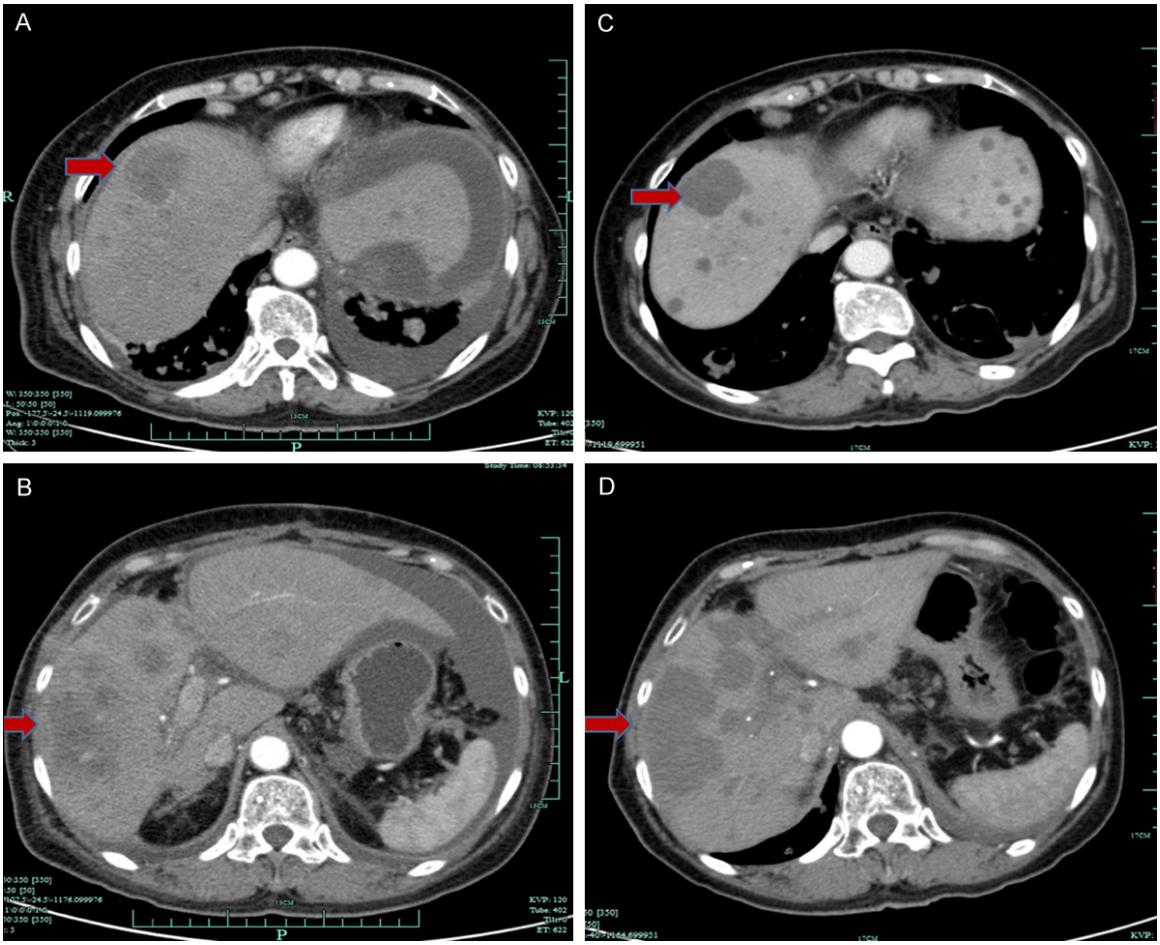

Figure 3. Total abdominal enhancement CT (A and B, December 12, 2017): multiple hepatic metastases and seroperitoneum were observed before apatinib treatment. Total abdominal enhancement CT (C and D, January 25, 2018): compared with the former total abdominal enhancement CT (A and B, December 12, 2017), the size of hepatic metastases are slightly diminished with an obvious decrease in blood supply after one-month treatment of apatinib (500 mg/d). Red arrow, tumor. Abbreviations: CT, computed tomography.

Since the Eastern Cooperative Oncology Group score was 2, chemotherapy was not performed on the patient. Based on the previous study reported [7], an advanced ICC patient treated with apatinib achieved progression-free survival of 8 months. From December 14, 2017, the patient started to take apatinib (500 mg/d qd) orally. Following one-month of therapy, the symptoms of abdominal distension and pain were relieved, and CT scans (**Figures 2C**, **2D**, **3C**, **3D**, January 24-25, 2018) suggested central cavitation in tumors. During the following treatment, the patient was observed with several side effects including bloody diarrhea, sore throat and skin ecchymosis. The dose of apatinib was then reduced to 250 mg qd. Chest CT images (**Figure 2E** and **2F**) on March 13, 2018 demonstrated increased and enlarged bilateral lung metastases accompanied by bilateral pleural effusion. Eventually, the disease progressed to death on March 24, 2018. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

ICC is usually diagnosed when the disease has already metastasized, by combining non- specific biomarkers and biopsy samples, as well as imaging methods. ICC can present three different patterns of growth: mass-forming, periductal infiltrating, and intra-ductal growing, in which the mass-forming ICC is the most frequent form. Occult HBV infection is an emerging risk factor for ICC [8]. The established stan-

dard chemotherapy for patients with metastatic ICC is cisplatin plus gemcitabine treatment [4].

Several signaling pathway are deregulated including JAK–IL-6-STAT3, EGFR, VEGFR, HGF/MET, RAS/MAPK, NOTCH and WNT, which are related to the inflammatory, stress response, tumor growth, and metastasis, and have been reported to be involved in ICC [3, 9]. It is widely accepted that angiogenesis plays a key role in tumor development. Vascular epidermal growth factor (VEGF) is a well-known central mediator of angiogenesis. Blocking the VEGF/VEGFR axis, leading to the inhibition of new blood vessel formation, proliferation and migration, is considered an efficient therapeutic approach against many tumors [10]. VEGFR-2, implicated in the vascular endothelial growth factor (VEGF), induces pathological formation of a leaky vasculature [11].

Apatinib, a specific molecular inhibitor of VEGFR-2, has been demonstrated antitumor activity both *in vivo* and *in vitro* and is a promising oral antiangiogenic agent for a broad range of malignancies, including gastric cancer, non-small-cell lung cancer, breast cancer, and hepatocellular carcinoma [10, 12-14]. As apatinib can inhibit tumor growth through suppressing VEGF signaling, it is supposed to be of great value in the treatment of ICC [15]. Nonetheless, few studies have applied apatinib for ICC treatment.

There has been another case reported about apatinib for treating advanced intrahepatic cholangiocarcinoma after failed chemotherapy with 6-month progression-free survival [16]. To the our best knowledge, this is the third case of advanced ICC treated with single apatinib. In this case, the patient achieved stable status with 3-month treatment of apatinib although accompanied with some adverse events, then the disease progressed to death likely due to the lack of optimization of the dose or development of drug resistance.

Conclusion

Apatinib can serve as an alternative option for the treatment of advanced ICC patients, particularly for those who have poor physical conditions and are unable to tolerate chemotherapy, through real-time monitoring the side effects and adjusting administration dose.

Disclosure of conflict of interest

None.

Abbreviations

ICC, intrahepatic cholangiocarcinoma; VEGFR-2, vascular endothelial growth factor receptor-2; VEGF, vascular endothelial growth factor; CT, computed tomography.

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