FGFR2-BICC1: A Subtype Of FGFR2 Oncogenic Fusion Variant In Cholangiocarcinoma And The Response To Sorafenib

Xihui Ying1
Jianfei Tu1
Wenxian Wang2
Xingliang Li3
Chunwei Xu4
Jiansong Ji1

1Department of Radiology, Lishui Central Hospital/Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Lishui, Zhejiang 323000, People’s Republic of China; 2Department of Chemoetherapy, Zhejiang Cancer Hospital, Hangzhou, Zhejiang 310022, People’s Republic of China; 3Department of Thoracic Disease Diagnosis and Treatment Center, Zhejiang Rongjun Hospital, Jiaxing, Zhejiang 314000, People’s Republic of China; 4Department of Pathology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian 350014, People’s Republic of China

Abstract: Fibroblast growth factor receptor (FGFR) family includes four highly conserved receptor tyrosine kinases. Particularly, FGFR2 has been identified as a potential target for tyrosine kinase inhibitor (TKI) treatment. Except for immunohistochemistry and fluorescence in situ hybridization, next-generation sequencing (NGS) technology represents a novel tool for FGFR2 detection that covers a wide range of fusion genes. In the present work, we present a case of cholangiocarcinoma who had FGFR2-BICC1 rearrangement detected by NGS. A 76-year-old female diagnosed with cholangiocarcinoma underwent four cycles of chemotherapy. The NGS assay showed that the tumor had a FGFR2-BICC1 rearrangement. The patient had a favorable tumor response to sorafenib. Herein, we report the first case with cholangiocarcinoma harboring FGFR2-BICC1 who is sensitive to sorafenib therapy.

Keywords: cholangiocarcinoma, NGS, FGFR2 rearrangement

Introduction
Cholangiocarcinoma is the second most diagnosed liver tumor next to hepatocellular carcinoma, which is characterized by its late diagnosis and poor prognosis. It is estimated that cholangiocarcinoma accounts about 3% of all gastrointestinal tumors and its overall 5-year survival rate was less than 10%.1,2 Current therapeutic options for cholangiocarcinoma include surgery and systematic chemotherapy. Standard chemotherapy treatment for cholangiocarcinoma is gemcitabine administered alone or in combination with cytotoxic agents such as cisplatin. However, patients underwent the above standard chemotherapy generally have a poor prognosis with a median survival of 6–12 months, highlighting the urgent need for more cholangiocarcinoma treatment modalities.3 Currently, some clinical trials utilizing target drugs in cholangiocarcinoma are under investigation. Most of the clinical trials focused on the efficacy of small molecule inhibitors targeting EGFR signaling pathway.4,5 The fibroblast growth factor receptor (FGFR) family includes four highly conserved receptor tyrosine kinases. FGFR2 have been reported as a novel target for tyrosine kinase inhibitor (TKI) treatment.6,7 Herein, we report a patient with cholangiocarcinoma who had a FGFR2-rearranged gene fusion and was sensitive to TKI-sorafenib, a multi-targeted small molecule.

Case Presentation
A written informed consent has been provided by the patient to have the case details and any accompanying images published and the study was approved by the Institutional Ethics Review Board of the hospital.
A 76-year-old female was admitted to our hospital in March 2011 because of a space-occupying lesion in the liver during routine physical examination. A magnetic resonance imaging (MRI) scan revealed intrahepatic multiple nodules in the right liver (Figure 1A). The patient underwent laparoscopy-guided liver biopsy for confirmation diagnosis. The patients were diagnosed with cholangiocarcinoma with immunohistochemical staining positive expression of CK19 and negative for HEP (Figure 2A). The patient was treated with floxuridine, oxaliplatin and pirarubicin in transcatheter hepatic arterial chemoembolization (TACE). After the TACE treatment, the patient also underwent the right hepatectomy under general anesthesia. Hematoxylin and eosin (H&E) staining confirmed a typical morphology of differentiated cholangiocarcinoma in the posterior portion of the right lobe, with invasion of the hepatic capsule and positive surgical margins (Figure 2B). Thus, the patient underwent floxuridine, oxaliplatin, pirarubicin and ultrafluid lipiodol, recombinant human interleukin in TACE in May 2011. Five years later, the disease progressed and patients subsequently underwent chemotherapy of gemcitabine cisplatin followed by hepatic support nutrition, i.e., intravenous injection with 80mg glycyrrhizin per day. On June 2018, the patient underwent lobaplatin and gemcitabine followed by hepatic support nutrition, i.e., intravenous injection with 80mg glycyrrhizin per day. However, the patient did not respond to the above treatment and disease progressed five months later (Figure 1B). Because of no response and disease progression, the patients underwent gene mutation examination. The NGS analysis of the peripheral blood revealed a FGFR2-BICC1 rearrangement, as shown in Figure 3 (3D Medicines, Shanghai China). In addition, immunohistochemistry analysis showed that FGFR2-BICC1

![Figure 1](https://www.dovepress.com/figure-1-magnetic-resonance-imaging-for-tumors-magnetic-resonance-imaging-mri-scans-were-performed-at-initial-diagnosed-a-and-before-b-and-c-and-after-d-sorafenib-therapy)
protein was highly expressed in cholangiocarcinoma (Figure 4). For effective mutation, the patient underwent oral sorafenib treatment in November 2018. After 1 month, the MRI scan showed a decrease in tumor size (Figure 1C). According to RECIST, the patient was considered to have a partial response (PR) to sorafenib (Figure 1D). During treatment with sorafenib, there were no adverse events such as rashes, gastrointestinal reactions, and cordis damage. Up to last follow-up, the disease is stable and the patient is being treated with sorafenib.

Discussion
Sorafenib is a multi-targeted small molecule that suppresses tumor proliferation and angiogenesis through inhibiting the activity of fibroblast growth factor, vascular endothelial growth factor receptor (VEGFR) 2/3, RAF proto-oncogene, serine/threonine kinase and platelet-derived growth factor receptor (PDGFR). Numerous animal models and clinical studies indicated that sorafenib exhibits a significant safety and efficacy against a variety of cancers. Sorafenib also had been approved for the treatment of renal cell and hepatocellular carcinoma. However, limited clinical data can be available on the efficacy of sorafenib in patients with advanced cholangiocarcinoma. Several case reports demonstrated potential benefits of sorafenib on cholangiocarcinoma. Clinical trials from a non-controlled and single-arm study showed that sorafenib only had limited effects for patients with cholangiocarcinoma. However, other studies revealed...
that sorafenib monotherapy had rather low efficacy in cholangiocarcinoma. Therefore, the precise clinical efficacy of sorafenib on cholangiocarcinoma needs further investigation. Selection of cholangiocarcinoma patients who may benefit from TKI treatment based on the molecular characteristics of tumor specimens is necessary for clinical treatment.

FGFR genes are involved in multiple biological processes, including cell transformation, angiogenesis, apoptosis, embryonic development, and tissue repair. Mutations and amplification of FGFR gene members have been shown to serve as therapeutic targets in a wide range of human malignancies, such as gastric, lung, and bladder cancers. Previous studies have demonstrated that overexpression of FGFR fusion proteins promotes tumor cell proliferation and migration. Bladder cancer cells harboring FGFR3 fusion proteins were shown to be more susceptible to pharmacologic inhibition both in vitro and in vivo. Transcriptome sequencing in patients with metastatic cholangiocarcinoma reveals novel genetic rearrangement, including FGFR2-BICC1, which was further confirmed by real-time PCR.

Bicc1 gene encodes a RNA-binding protein and has been identified in many species, ranging from C. elegans to humans. Loss of Bicc1 in Drosophila disrupts the anterior follicle cell migration and affects anterior-posterior patterning, leading to embryos development disorder. Knockdown of the zebrafish homologue of Bicc1 induces cystic kidneys in vivo. Recently, the association between Bicc1 level and various mood disorders are demonstrated in animals and humans. It remains to be determined whether patients with FGFR2-BICC1 fusion exhibit unique clinicopathologic manifestations.

In conclusion, the present case provides a first report of a cholangiocarcinoma patient harboring FGFR2-BICC1 fusion who are responded to sorafenib therapy, suggesting the critical role for the diagnostic application of NGS in precision medicine.

Disclosure
The authors report no conflicts of interest in this work.
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