

# World Journal of *Gastroenterology*

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**EDITORIAL**

- 4135** Attenuated adenomatous polyposis of the large bowel: Present and future  
*Roncucci L, Pedroni M, Mariani F*
- 4140** Evolution of associating liver partition and portal vein ligation for staged hepatectomy: Simpler, safer and equally effective methods  
*Peng SY, Wang XA, Huang CY, Zhang YY, Li JT, Hong DF, Cai XJ*

**REVIEW**

- 4146** Antioxidant dietary approach in treatment of fatty liver: New insights and updates  
*Ferramosca A, Di Giacomo M, Zara V*
- 4158** *Helicobacter pylori* BabA in adaptation for gastric colonization  
*Ansari S, Yamaoka Y*

**MINIREVIEWS**

- 4170** Advances in surgical management for locally recurrent rectal cancer: How far have we come?  
*Lee DJK, Sagar PM, Sadadcharam G, Tan KY*

**ORIGINAL ARTICLE****Basic Study**

- 4181** Anti-steatotic and anti-fibrotic effects of the KCa3.1 channel inhibitor, Senicapoc, in non-alcoholic liver disease  
*Paka L, Smith DE, Jung D, McCormack S, Zhou P, Duan B, Li JS, Shi J, Hao YJ, Jiang K, Yamin M, Goldberg ID, Narayan P*
- 4191** Induction of chronic cholestasis without liver cirrhosis - Creation of an animal model  
*Dondorf F, Fahrner R, Ardelt M, Patsenker E, Stickel F, Dahmen U, Settmacher U, Rauchfuß F*
- 4200** Solid lipid nanoparticles delivering anti-inflammatory drugs to treat inflammatory bowel disease: Effects in an *in vivo* model  
*Dianzani C, Foglietta F, Ferrara B, Rosa AC, Muntoni E, Gasco P, Della Pepa C, Canaparo R, Serpe L*
- 4211** Relevance of proteolysis and proteasome activation in fatty liver graft preservation: An Institut Georges Lopez-1 vs University of Wisconsin appraisal  
*Zaouali MA, Panisello-Roselló A, Lopez A, Castro Benítez C, Folch-Puy E, García-Gil A, Carbonell T, Adam R, Roselló-Catafau J*

- 4222** Naturally occurring mutations in the reverse transcriptase region of hepatitis B virus polymerase from treatment-naïve Korean patients infected with genotype C2

*Kim JE, Lee SY, Kim H, Kim KJ, Choe WH, Kim BJ*

- 4233** Inhibition of N-methyl-N-nitrosourea-induced gastric tumorigenesis by Liuwei Dihuang Pill in db/db mice

*Zhuang S, Jian YM, Sun YN*

- 4243** miR-382 functions as a tumor suppressor against esophageal squamous cell carcinoma

*Feng J, Qi B, Guo L, Chen LY, Wei XF, Liu YZ, Zhao BS*

### **Case Control Study**

- 4252** Pancreas preserving distal duodenectomy: A versatile operation for a range of infra-papillary pathologies

*Mitchell WK, Thomas PF, Zaitoun AM, Brooks AJ, Lobo DN*

### **Retrospective Study**

- 4262** Clinical importance of colonoscopy in patients with gastric neoplasm undergoing endoscopic submucosal dissection

*Tsuchida C, Yoshitake N, Kino H, Kaneko Y, Nakano M, Tsuchida K, Tominaga K, Sasai T, Masuyama H, Yamagishi H, Imai Y, Hiraishi H*

- 4270** Outcomes of right-lobe and left-lobe living-donor liver transplantations using small-for-size grafts

*She WH, Chok KSH, Fung JYY, Chan ACY, Lo CM*

### **Clinical Trials Study**

- 4278** Potential application of neogalactosylalbumin in positron emission tomography evaluation of liver function

*Du SD, Li SH, Jin B, Zhu ZH, Dang YH, Xing HQ, Li F, Wang XB, Lu X, Sang XT, Yang HY, Zhong SX, Mao YL*

### **Observational Study**

- 4285** Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn's disease

*Thomassin L, Armengol-Debeir L, Charpentier C, Bridoux V, Koning E, Savoye G, Savoye-Collet C*

- 4293** New totally intracorporeal reconstructive approach after robotic total gastrectomy: Technical details and short-term outcomes

*Parisi A, Ricci F, Gemini A, Trastulli S, Cirocchi R, Palazzini G, D'Andrea V, Desiderio J*

### **EVIDENCE-BASED MEDICINE**

- 4303** Substantial hepatic necrosis is prognostic in fulminant liver failure

*Ndekwe P, Ghabril MS, Zang Y, Mann SA, Cummings OW, Lin J*

**CASE REPORT**

- 4311** Benefit of everolimus in treatment of an intrahepatic cholangiocarcinoma patient with a *PIK3CA* mutation

*Bian JL, Wang MM, Tong EJ, Sun J, Li M, Miao ZB, Li YL, Zhu BH, Xu JJ*

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## Benefit of everolimus in treatment of an intrahepatic cholangiocarcinoma patient with a *PIK3CA* mutation

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**Author contributions:** Bian JL and Wang MM followed the patient; Miao ZB, Li YL, Zhu BH and Xu JJ provided genetic analysis for the variants tested in the patient; Tong EJ, Sun J and Li M searched related articles; Bian JL and Li YL wrote the paper; all authors have read and approved the final manuscript.

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### Abstract

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare form of liver cancer with a poor prognosis. The therapeutic options for patients with advanced ICC are limited and usually ineffective. There is currently no approved targeted therapy for ICC, although accumulating evidence supports inhibition of the PI3K/Akt/mTOR signaling pathway as a promising therapeutic strategy in the treatment of ICC. Here, we report a patient with stage IV ICC harboring a *PIK3CA* mutation who responded well to the mTOR inhibitor everolimus. Computed tomography and magnetic resonance imaging demonstrated shrinkage of the tumor and maintenance of a partial response for 6.5 mo after everolimus treatment as the best response. To the best of our knowledge, this is the first clinical case report in the literature of clinical benefit from everolimus treatment in an ICC patient with *PIK3CA* mutation.

**Key words:** Everolimus; Next generation sequencing; *PIK3CA*; Intrahepatic cholangiocarcinoma

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**Core tip:** We report a stage IV intrahepatic cholangiocarcinoma (ICC) patient harboring a *PIK3CA* mutation who responded well to the mTOR inhibitor everolimus. Computed tomography and magnetic resonance imaging demonstrated shrinkage of the tumor and the maintenance of partial response for 6.5 mo after everolimus treatment as the best response. To the best of our knowledge, this is the first clinical case report in the literature of an ICC patient with *PIK3CA* mutation deriving benefit from everolimus treatment.

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## INTRODUCTION

Cholangiocarcinoma, the second most common primary malignancy of the liver, is divided into four categories based on the anatomic location of origin within the biliary system as follows: intrahepatic, hilar, distal biliary, and ampullary<sup>[1,2]</sup>. Complete surgical resection remains the only potentially curative option for patients with intrahepatic cholangiocarcinoma (ICC). However, because most cases are diagnosed at advanced stages, only one-third of ICC tumors are amenable for surgical resection with a 5-year survival rate of 20%-40%<sup>[3,4]</sup>, and unresectable ICC carries a dismal prognosis. Systemic chemotherapy, conventional external beam radiation, and brachytherapy are established standard treatments but show limited success and are associated with toxicity<sup>[2]</sup>.

Doublet gemcitabine and cisplatin therapy is currently proposed as the standard first-line therapy for patients with an advanced disease; however, the efficiency is limited<sup>[5]</sup>. Locoregional therapy appears to have a better effect against ICC<sup>[6]</sup>, but more data are needed to define its role. To date there has been no approved targeted molecular therapy for ICC and identification of a definitive treatment remains an unmet need. Recently, the use of next-generation sequencing (NGS) technologies has enabled the identification of frequently observed actionable molecular alterations that hold the promise of improving the management of advanced ICC patients.

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway plays an essential role in regulating cell survival and proliferation<sup>[6]</sup>. Mutation in *PIK3CA* has been reported in 8% of ICC patients according to The Cancer Genome Atlas (TCGA) database, and activating mutations of *PIK3CA* that are related to tumorigenesis and cancer progression have been identified in a broad spectrum of malignant tumors<sup>[7,8]</sup>. Therefore, inhibition of the mTOR pathway represents a promising therapeutic strategy in the treatment of ICC. Everolimus is a novel macrolide derivative of rapamycin that inhibits mTOR and was approved by the Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma<sup>[9]</sup> and other cancer types<sup>[10]</sup>. However, whether everolimus is effective against ICC is unknown. In studies of ICC-related cancers, *in vitro* and *in vivo* results demonstrated that everolimus exhibits cytotoxic and antimetastatic effects in a cholangiocarcinoma cell line<sup>[11]</sup>. These results suggest that everolimus may be a potential therapeutic agent for the treatment of

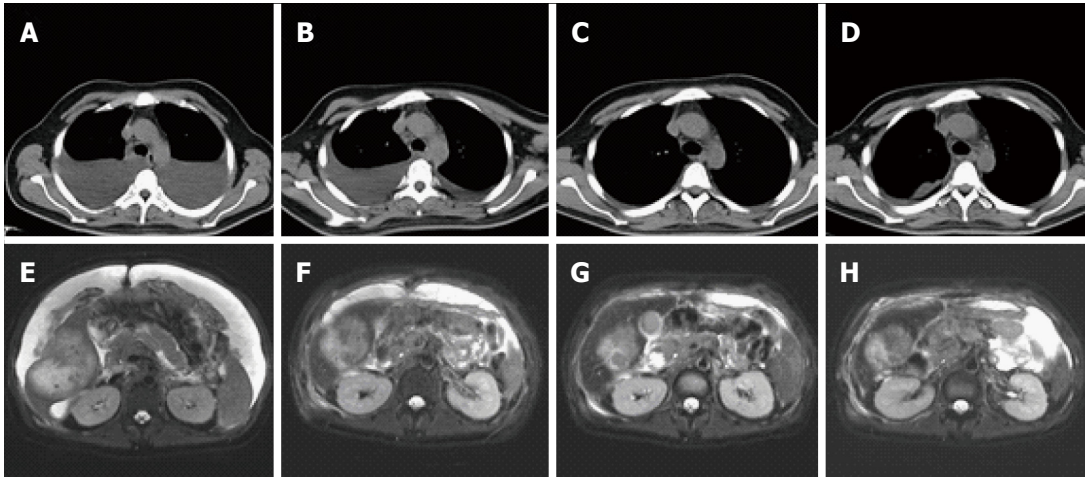
patients with ICC possessing an aberrant PI3K/Akt/mTOR signaling pathway.

Here, we report a patient with stage IV ICC harboring a *PIK3CA* mutation who responded well to the mTOR inhibitor everolimus, demonstrating that inhibition of the PI3K/Akt/mTOR signaling pathway is a promising therapeutic avenue for ICC. To the best of our knowledge, this is the first clinical case report in the literature of an ICC patient with *PIK3CA* mutation deriving benefit from everolimus treatment.

## CASE REPORT

A 31-year-old Chinese man presented with 1-mo history of progressive abdominal distension and was admitted to hospital. A computed tomography (CT) scan revealed a space-occupying mass in the liver with massive peritoneal effusion and some pleural effusion in both sides of the chest. The patient had no history of alcohol abuse, hepatitis, or cirrhosis, and denied any family history of cancers and other hereditary diseases. He was transferred to our hospital in December 2015. Physical examination revealed a distended abdomen with tenderness and muscle guarding, and his abdominal girth was measured at 105 cm. No icteric sclera or xanthochromia was detected, and the Murphy's sign was negative. Liver function test indicated that the levels of total protein and albumin were 57.6 g/L and 32.4 g/L, respectively, which were below normal and indicated malnutrition and hypoalbuminemia, whereas bilirubin and aminotransferase were within the normal range. The tumor markers carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), cancer antigen 19-9 (CA19-9), and carbohydrate antigen 72-4 (CA72-4) were all within the normal range. Further magnetic resonance imaging (MRI) of the liver showed a 9.9 cm × 7.4 cm mass at the posterior right lobe of the liver with multiple swollen retroperitoneal lymph nodes and massive peritoneal effusion (Figure 1A and E). The Eastern Cooperative Oncology Group (ECOG) performance score was 2-3. Abdominal paracentesis was performed repeatedly to relieve abdominal distension, which was also used to collect exfoliated tumor cells from the ascites for cytological diagnosis; however, no tumor cells were detected. Consequently, core needle biopsy of the liver mass was performed and the specimens were sent for pathological evaluation, which indicated a poorly differentiated adenocarcinoma. Immunohistochemical staining showed that the cells were positive for CK7, CK19, CK8, and CEA and negative for glypican-3, hepatocyte marker, and vimentin. These results suggested a diagnosis of stage IV ICC (cT3N1M1).

There is currently no standard treatment for ICC, and chemotherapy is generally ineffective. This patient was not suitable for chemotherapy due to his poor physical condition, therefore he was recommended for NGS to identify possible therapeutic targets. His liver



**Figure 1** Computed tomography and magnetic resonance imaging scans show that, compared to the baseline (A and E), the patient's peritoneal effusion decreased after 3 cycles of chemotherapy treatment (B and F), tumor shrank after everlimus treatment for 2 mo (C and G), and stable disease was achieved after everlimus treatment for 4 mo (D and H).

biopsy specimen and matched blood sample were sent for NGS panel analysis after consent was obtained from the patient himself and his family. We detected all genomic alteration types, including base substitutions, insertions and deletions, copy number alterations, and rearrangements, for more than 390 genes commonly associated with cancers. While we were waiting for the NGS results, intraperitoneal chemotherapy with cisplatin plus Endostar was initiated for the control of ascites. The patient was perfused with three cycles of cisplatin 30 mg in 250 mL of normal saline (NS) and Endostar 60 mg in 250 mL of NS every 5 d. Amino acids, fat emulsion, and albumin were added during the treatment for nutritional support. Before the first intraperitoneal chemotherapy the patient felt aggravated chest stuffiness and a CT scan demonstrated increased pleural effusion. After three cycles of treatment, the patient's abdominal girth decreased from 105 cm to 85 cm and the CT scan indicated decreased peritoneal effusion (Figure 1B and F).

In January 2016, the genomic profile of the patient revealed three somatic mutations, including E545G mutation of the *PIK3CA* gene (NM\_006218), R132C mutation of the *IDH1* gene (NM\_005896) and c.714+1G>T mutation of the *PBRM1* gene (NM\_018313). As preclinical data suggest that activating mutations in *PIK3CA* may predict a sensitivity to inhibitors of the PI3K/AKT/mTOR pathway<sup>[11]</sup>, the patient received everolimus (10 mg orally daily), provided off-label with insurance approval. CT scans showed a notable decrease in pleural effusion and tumor shrinkage after everolimus treatment for 2 mo (Figure 1C and G). One month after everolimus treatment, the levels of total protein and albumin increased to 76.2 g/L (normal range, 63–82 g/L) and 42.9 g/L (normal range, 35–50 g/L), respectively, and the ECOG performance score was evaluated as 1. MRI showed shrinkage of the tumor from 9.9 cm × 7.4 cm to 6.4 cm × 4.3 cm, which was considered a partial response (PR)

according to Response Evaluation Criteria in Solid Tumors criteria.

In May 2016, the patient suddenly displayed icterus, icteric sclera, and xanthochromia. On May 8, the levels of total bilirubin, direct bilirubin, indirect bilirubin, and ammonia increased to 145, 122, 23, and 64  $\mu$ mol/L, respectively. Serum levels of alanine transaminase (ALT) and aspartate aminotransferase (AST) levels were 404 and 321 U/L and those of total protein and albumin were 76 and 42 g/L, respectively. His abdominal girth increased from 85 cm to 87 cm, and color Doppler ultrasound demonstrated a slight increase in pleural and peritoneal effusion (Figure 1D and H). The Child-Pugh score of the patient was classified as Class B, therefore the everolimus dosage was decreased to 5 mg orally once daily (half the standard dose) from May 10 with consideration of his liver dysfunction. Magnetic resonance cholangiopancreatography showed a high-position biliary obstruction, and local three-dimensional conformal radiotherapy (3DCRT) was started on May 16. However, the 3DCRT was ineffective because the icteric index and liver function showed continued aggravation with no improvement in biliary obstruction. On May 30, surgical biliary drainage was performed to reduce icterus. The patient continued to receive everolimus (5 mg once daily) to the present time. At the latest follow-up on July 16, the tumor response remained as stable disease and the progression-free survival (PFS) had lasted for more than 6.5 mo from the initial treatment with everolimus.

## DISCUSSION

Genomic profiling of the patient revealed three somatic mutations: E545G mutation of *PIK3CA* and mutations of *IDH1* and *PBRM1* genes. Activating mutations in the region encoding the p110 $\alpha$  subunit of PI3K (*PIK3CA*) have been identified in a broad spectrum of



malignant tumors. Codon 545 is a hotspot for *PIK3CA* mutations that are known to activate the PI3K/Akt/mTOR signaling pathway<sup>[12,13]</sup>. However, the E545K substitution is much more common in cancers than the E545G mutation; E545K represents 25% of all *PIK3CA* mutations<sup>[14]</sup> whereas E545G has only been reported in a few carcinomas<sup>[15]</sup>. *In vitro* research studies comparing the activity of mutant *PIK3CA* proteins have shown that the E545G substitution displays strong transforming activity in chicken embryo fibroblasts, although its effect is lower than that of the more common E542K and E545K substitutions<sup>[16]</sup>.

Both the *IDH1* and *PBRM1* genes are recurrently mutated in ICC with frequencies of 4.9% and 18%, respectively<sup>[17]</sup>. Mutations in *IDH1* and *IDH2* are confined to the active site and result in the production of a neomorphic metabolite 2-hydroxyglutarate (2HG), which is normally found in scarce amounts, through NADPH-dependent reduction of 2-OG to the R enantiomer of 2HG. Frequent somatic hotspot mutations in *IDH1* have been identified in gliomas, chondrosarcomas, myeloid leukemias, and other cancers. Suppression of endogenous mutant *IDH1* expression was recently reported in HT180, a fibrosarcoma cell line with a native *IDH1* R132C heterozygous mutation<sup>[18]</sup>. *PBRM1* is associated with chromatin remodeling and is crucial for the suppression of aggressive clear cell renal cell carcinoma (ccRCC) tumors<sup>[19]</sup>. However, there are no preclinical or early clinical data implicating *IDH1* and *PBRM1* as biomarkers for targeted cancer therapy in ICC.

The mTOR inhibitor everolimus has been approved by the FDA for the treatment of advanced RCC, subependymal giant cell astrocytoma (SEGA), and progressive neuroendocrine tumors (PNET) of pancreatic origin as monotherapy, and of advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane. The effect of everolimus is clearly proven in many cancers, especially those with *PIK3CA* mutations. Phase III clinical trials suggested that patients with HER2-positive advanced breast cancer with *PIK3CA* mutations could derive a PFS benefit from everolimus<sup>[20]</sup>. Recent research demonstrated that mTOR pathway activating mutations confer sensitivity to everolimus regardless of cancer type<sup>[21]</sup>. A case report supported the use of everolimus monotherapy in a patient with refractory metastatic gastric cancer harboring *PIK3CA* and p53 aberrations<sup>[22]</sup>. In our case study, everolimus exhibited good efficacy in an ICC patient. The adverse effects of everolimus on liver dysfunction may be a cause for concern. In May 2011 the FDA approved everolimus for the treatment of PNET of pancreatic origin. The approval was based on a randomized controlled trial of everolimus 10 mg/d (*n* = 207) vs placebo (*n* = 203) in patients with unresectable, locally advanced, or metastatic pancreatic neuroendocrine tumors. The median PFS for patients treated with everolimus was 11.0 mo vs 4.6 mo for patients treated with

placebo. However, deaths occurred in seven patients treated with everolimus and one patient treated with placebo<sup>[23]</sup>. The causes of death in patients treated with everolimus included one case with hepatic failure. Although there is no direct evidence that everolimus is related to hepatic failure, hepatobiliary patients should be kept under strict surveillance when taking everolimus.

Generally speaking, ICC is a relatively rare cancer, accounting for 3% of gastrointestinal malignancies, and has a poor prognosis. The limited number of patients leads to a lack of clinical trials conducted specifically in ICC patients, which precludes the generation of clinical practice guidelines establishing a "standard of care" for these patients. At present, the prognosis for patients diagnosed with unresectable ICC is poor, with a life expectancy of approximately 1 year and actuarial probability of survival of 5% at 5 years with traditional chemotherapy<sup>[2,24]</sup>. To date, no molecular targeted therapy has been proven effective for ICC. To the best of our knowledge, this is the first clinical case report in the literature of benefit from everolimus treatment in an ICC patient with a *PIK3CA* mutation. This patient is still considered progression-free with good quality of life at the latest follow-up, highlighting the potential of the PI3K/Akt/mTOR signaling pathway as a therapeutic target in ICC.

To our knowledge, this case represents the first report of an ICC patient with a *PIK3CA* mutation who derived benefit from everolimus treatment. However, whether the presence of mutation of *IDH1* and *PBRM1* contributed to the patient's response to targeted therapy is unclear, and the reason for the patient's response to everolimus and prolonged survival has yet to be elucidated.

## COMMENTS

### Case characteristics

A 31-year-old Chinese man presented with 1-mo history of progressive abdominal distension and was admitted to hospital.

### Clinical diagnosis

Physical examination revealed a distended abdomen with tenderness and muscle guarding, and his abdominal girth was measured at 105 cm.

### Differential diagnosis

Hepatocellular carcinoma, intrahepatic cholangiocarcinoma, stage IV intrahepatic cholangiocarcinoma (cT3N1M1).

### Laboratory diagnosis

Liver function test indicated that the levels of total protein and albumin were 57.6 g/L and 32.4 g/L, respectively, which were below normal and indicated malnutrition and hypoalbuminemia, whereas bilirubin and aminotransferase were within the normal range. The tumor markers carcinoembryonic antigen, alpha-fetoprotein, cancer antigen 19-9, and carbohydrate antigen 72-4 were all within the normal range.

### Imaging diagnosis

A computed tomography (CT) scan revealed a space-occupying mass in the liver with massive peritoneal effusion and some pleural effusion in both sides of

the chest.

### Pathological diagnosis

Pathological examination revealed intrahepatic cholangiocarcinoma (ICC).

### Treatment

The genomic profile of the patient revealed three somatic mutations, including E545G mutation of the *PIK3CA* gene, R132C mutation of the *IDH1* gene and c.714+1G>T mutation of the *PBRM1* gene. Based on the gene alteration testing report and the clinical trial studies, the patient received everolimus (10 mg orally daily), provided off-label with insurance approval.

### Term explanation

The mTOR inhibitor everolimus has been approved by the FDA for the treatment of advanced RCC, subependymal giant cell astrocytoma, and progressive neuroendocrine tumors of pancreatic origin as monotherapy, and of advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane. To the best of our knowledge, this is the first clinical case report in the literature of an ICC patient with a *PIK3CA* mutation deriving benefit from everolimus treatment.

### Experiences and lessons

Results observed in this case encourage further research on the activity of everolimus in ICC, based on the presence of *PIK3CA* mutation. This could lead to a selection of ICC patients to be treated with this drug, and could help identify a novel treatment strategy for *PIK3CA*-mutated ICC patients.

### Peer-review

Very interesting case report. In this study, the authors report a stage IV ICC patient harboring a *PIK3CA* mutation who responded well to the mTOR inhibitor everolimus.

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