Olaparib effectively treats local recurrence of extrahepatic cholangiocarcinoma in a patient harboring a *BRCA2*-inactivating mutation: a case report

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Abstract: Cholangiocarcinoma (CCA) is a malignant tumor with poor prognosis and high recurrence rate. There is no standard treatment for advanced CCA beyond first-line chemotherapy, which provides only limited benefits. In this study, we report a case of a postoperative recurrence ECC patient harboring a breast cancer 2 (*BRCA2*)-inactivating rearrangement mutation that had an obvious reaction to olaparib therapy. The patient was a 68-year-old man with postoperative recurrence of extrahepatic CCA (ECC) who declined systemic chemotherapy. In August 2015, abdominal computed tomography (CT) of the patient revealed intrahepatic bile duct dilatation, obstruction at the hepatic hilar region proximal to the common hepatic duct, and splenomegaly, and radical surgical resection was performed. Postoperative histopathology diagnosis was ECC without metastases. In February 2017, abdominal CT revealed local recurrence, and the patient refused chemotherapy. *BRCA2* rearrangement were detected by next-generation sequencing. Oral administration of olaparib was initiated. The patient achieved stable disease 1 month later, progression-free survival for >10 months without any significant adverse reactions, and an overall survival (OS) of 27 months. This is the first report demonstrating the clinical benefits of olaparib in a *BRCA2* rearrangement-harboring patient with ECC. This observation would help determine the best treatment option for advanced ECC patients.

Keywords: Extrahepatic cholangiocarcinoma (ECC); breast cancer 2 (*BRCA2*)-inactivating rearrangement; olaparib; next-generation sequencing; case report

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Introduction

Cholangiocarcinoma (CCA), stratified anatomically into intrahepatic CCA (ICC) and extrahepatic CCA (ECC), is a malignant tumor with poor prognosis and high recurrence rate (1). CCA is infrequently observed in Europe and the USA; however, it is more common in China (>6/100,000 cases) (2). Surgery remains the primary treatment option for biliary tract cancers; however, it is considered unsuitable for more than two-thirds of CCA patients (3). There are few chemotherapeutic options that provide only limited benefits for advanced patients according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines. Given the emerging evidence regarding the actionable targets for treating CCA, molecular testing of unresectable or metastatic tumors is recommended (4). At present, targeted therapies, including larotrectinib and entrectinib for *NTRK* gene fusion-positive

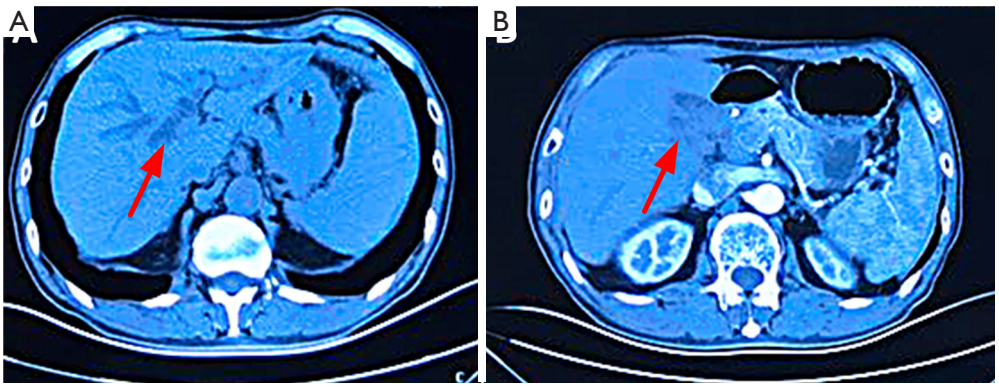

Figure 1 Abdominal computed tomography (CT). (A) Preoperation: CT revealed intrahepatic bile duct dilatation, obstruction at the hepatic hilar region proximal to the common hepatic duct, and splenomegaly (arrow). (B) Baseline: abdominal CT revealed local recurrence: hepatic hilar mass, involving the hepatic artery and portal vein, and dilated bile duct in the hepatic hilum and left lobe of the liver (arrow).

tumors (5,6), and pembrolizumab for MSI-H/dMMR tumors are recommend for advanced CCA (7). As pemigatinib has great therapeutic potential in previously treated patients with CCA who have *FGFR2* fusions or rearrangements and was accelerated approved by the US Food and Drug Administration (FDA) (8), and ivosidenib was demonstrated efficacy and safety in advanced, *IDH1*-mutant CCA (9), these 2 target therapies are recommended for the treatment of CCA in the latest NCCN guidelines.

BRCA2 inactivation plays an important role in hepatocellular carcinoma development and progression, and patients with mutant *BRCA2* alleles are more likely to develop malignant liver tumors (10). *BRCA2*-inactivating mutation frequency in ECC is approximately 4% (11). Few reports of *BRCA2*-inactivating gene rearrangements exist for bile duct carcinoma. In the present study, we reported a case of a postoperative recurrence ECC patient harboring a *BRCA2*-inactivating rearrangement mutation that had an obvious reaction to olaparib therapy. We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3681).

Case presentation

In June 2015, a 68-year-old man presented yellow discoloration of the skin without an obvious etiology, accompanied by nausea and bloating. He did not receive any treatment initially, and the skin discoloration gradually became more pronounced. In August 2015, the patient was treated at Liaoning Cancer Hospital and Institute, Shenyang, China. Abdominal computed tomography (CT) revealed intrahepatic bile duct dilatation, obstruction at the hepatic hilar region proximal to the common hepatic duct, and splenomegaly (*Figure 1A*). The patient underwent radical surgical resection for CCA. Postoperative pathological assessment revealed a moderately differentiated adenocarcinoma (1.5-cm diameter) arising from the bile duct and infiltrating the serosa, nerve involvement, and vascular tumor thrombus. Immunohistochemistry showed that the tumor comprised CK7+, CK20–, P53+ (~90%), and Ki-67+ (~90%) cells; ECC without metastases was diagnosed. The patient refused adjuvant therapy after surgery due to personal reasons. In February 2017, abdominal CT revealed local recurrence (*Figure 1B*). The patient refused chemotherapy because he was not experiencing discomfort.

In May 2017, surgically resected tissues were examined for 450 tumor-associated genes by OrigiMed (Shanghai, China) (*Table 1*) (2). Nine tumor-related gene variants were detected by next-generation sequencing, including a *BRCA2* rearrangement, cyclin-dependent kinase inhibitor 2A (*CDKN2A*) P81L, tumor protein p53 (*TP53*) Y163C, and ataxia-telangiectasia and rad3 related (*ATR*) K1557Sfs*8 mutations, as well as kirsten rat sarcoma (*KRAS*), C-X-C chemokine receptor type 4 (*CXCR4*), myeloid cell leukemia 1(*MCL1*), Fos proto-oncogene (*FOS*), and Jun proto-oncogene (*JUN*) amplifications.. *BRCA2* rearrangement was observed between chromosome 20 p11.21 and exons 21–27 of *BRCA2* (*Figure 2*), and might have had deletions of exons 1–20, thereby impairing *BRCA2* function.

In October 2017, the patient complained of upper abdominal pain and refused radiotherapy or chemotherapy.

Oral olaparib administration was initiated. Efficacy evaluation 1 month after treatment confirmed stable disease (*Figure 3A*). Until August 2018, the patient continued to benefit from olaparib treatment, and the disease remained stable without significant adverse reactions, such as anemia, vomiting, diarrhea, infection, or fatigue (*Figure 3B*) (12). The patient achieved progression-free survival (PFS) of >10 months, exceeding the 8-month median PFS obtained with the gemcitabine + cisplatin regimen recommended by the NCCN (13). During the first 10 months of taking olaparib, the patient was followed closely. However, the patient then returned to his hometown and we were unable to conduct further treatment or obtain imaging data. In January 2020, we were informed that the patient had died, with an overall survival (OS) of 27 months.

This case report shows that genetic testing for patients with biliary tract cancer, and olaparib treatment of patients with ECC harboring *BRCA2* rearrangements, are likely to be beneficial in clinical settings.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Table 1 Results of gene variations detected by next-generation sequencing

Gene	Mutation	Variation frequency
CDKN2A	P81L	35%
BRCA2	Rearrangement	–
KRAS	Amplification	–
TP53	Y163C	31%
ATR	K1557Sfs*8	3%
CXCR4	Amplification	–
MCL1	Amplification	–
FOS	Amplification	–
JUN	Amplification	–

*, stands for termination codon.

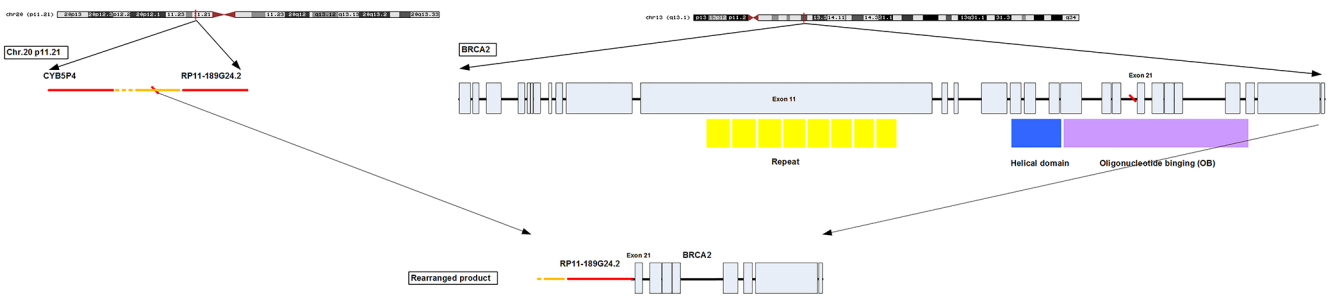

Figure 2 Schematic representation of the genomic rearrangement involving Chr.20 p11.21 and *BRCA2*.

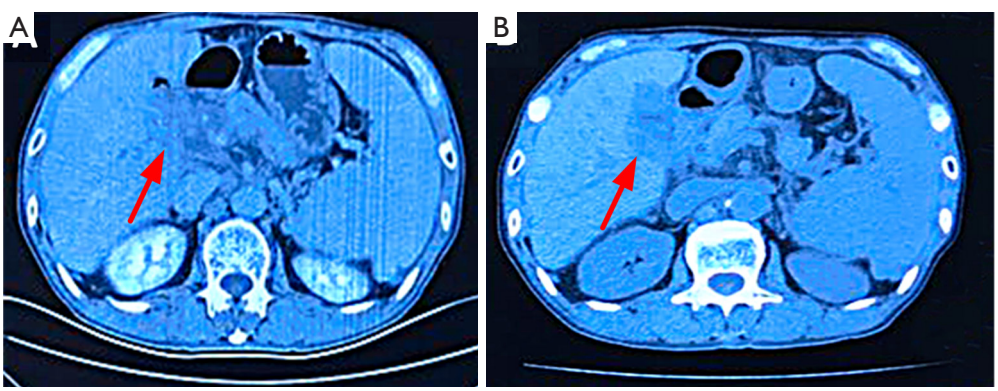

Figure 3 Abdominal computed tomography (CT). (A,B) Efficacy evaluation: 1 month and 10 months after treatment, stable disease (SD) was confirmed. Arrow indicated the hepatic hilar mass.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

BRCA1 and *BRCA2* are tumor-suppressor genes and play important roles in homologous recombination-mediated, double-stranded DNA break repair, thereby maintaining genomic stability. The mutant status of these genes can increase the risk of breast, ovarian, and gastric cancers. The FDA has approved the use of poly (ADP-ribose) polymerase (PARP) inhibitors, olaparib, talazoparib, rucaparib, and niraparib, for patients with breast and ovarian cancers involving *BRCA* mutations, and platinum-sensitive pancreatic and epithelial ovarian, fallopian tube, or primary peritoneal cancers.

Tumor cells with homologous recombination defects due to BRCA loss of function are more dependent on PARP-mediated DNA repair. Preclinical studies have demonstrated that PARP inhibitors can kill homologous recombination-defective tumor cells through a synthetic lethal mechanism (14,15). Among small-cell lung cancer patients with a *BRCA1/2* mutation (n=23) who received PARP inhibitor (talazoparib) monotherapy, 2 patients achieved partial remission and 4 achieved disease stabilization (16). Additionally, a refractory ICC patient with a heterozygous germline *BRCA2* p.S2670* mutation achieved partial response from olaparib monotherapy (17). The clinical effectiveness of PARP inhibitors for treating CCA patients with *BRCA* somatic mutations remains unclear. In the present study, we first reported the clinical benefits of olaparib in an ECC patient harboring a *BRCA2*-inactivating rearrangement.

The tumor suppressor gene, *CDKN2A*, encodes 2 unrelated proteins, p16INK4a and p14ARF (18). p16INK4a or p14ARF loss of function through mutations in *CDKN2A*, or via promoter hypermethylation, disturbs Rb/CDK and p53 signaling, resulting in uncontrolled cell growth and cancer (19). *CDKN2A* P81L causes a proline-to-leucine substitution at position 81 of p16INK4a. *In vitro* experiments have shown that the P81L mutation reduces the inhibitory effect of p16INK4a, prevents it from binding to CDK4 and inhibits protein activity. The mutant p16INK4a binds to CDK6 instead (20). A structural analysis showed that the mutant protein has folding defects (21).

There are no FDA-approved anticancer drugs targeting *CDKN2A* (p16INK4a). However, given that *CDKN2A* (p16INK4a) loss leads to CDK4/6 activation and cell proliferation, CDK inhibitors may represent a therapeutic option for cancer patients with *CDKN2A* loss-of-function variants. The FDA has approved the CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib for the treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer. Because the level of evidence between CDK4/6 inhibitors and molecular markers is lower compared with PARP inhibitors, CDK 4/6 inhibitors were not considered in this case.

TP53 encodes transcription factor p53 and is the most frequently mutated tumor-suppressor gene in human malignancies (22). *In vitro* experiments have shown that Y163C mutations decrease the transactivation capacity of p53, rendering the protein unable to suppress cell proliferation and induce apoptosis (23).

The DNA damage repair gene, *ATR*, encodes a serine/threonine kinase. The *ATR* K1557Sfs*8 mutation causes a lysine-to-serine conversion at position 1557, and the 8th codon is terminated in the new reading frame. Based on the location of the premature termination codon, it is predicted that this mutation leads to nonsense mutation-mediated mRNA degradation, and therefore, a lack of ATR protein.

RAS oncogenes, *NRAS*, *KRAS*, and *HRAS*, are commonly mutated in human tumors. *KRAS* amplification is observed in various tumors and is associated with increased levels of KRAS protein (24,25), which can in turn cause malignant transformation of cells through the activation of mitogen-activated protein kinase/extracellular signal-regulated kinase signaling (26). Unfortunately, there are no FDA-approved anticancer drugs targeting *TP53*, *ATR*, or *KRAS*. There are also no drugs targeting *CXCR4*, *MCL1*, *FOS*, and *JUN* amplifications in cancer.

In the present study, we reported on a patient with ECC harboring a *BRCA2*-inactivating rearrangement mutation responded to olaparib therapy with a PFS of >10 months and an OS of 27 months. This is the first report demonstrating the clinical benefits of olaparib in a patient with ECC harboring a *BRCA2* rearrangement. This case also highlights the importance of next-generation sequencing for providing valuable information for designing effective targeted therapies for ECC. Evidence-based decisions help determine the best customized treatment option.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-3681

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3681). JS, ML, and MX are from Shanghai OrigiMed Co. Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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