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**Response to olaparib in *BRCA1*-mutated gallbladder cancer: A case report**

Xie Y *et al*. *BRCA1*-mutated gallbladder cancer

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**Abstract**

Gallbladder cancer (GBC), although considered as a relatively rare malignancy, is the most common neoplasm of the biliary tract system. The late diagnosis and abysmal prognosis present challenges to treatment. The overall 5-year survival rate for metastatic GBC patients is extremely low. *BRCA1* and *BRCA2* are the breast cancer susceptibility genes and their mutation carriers are at a high risk for cancer development, both in men and women. Olaparib, an oral poly ADP-ribose polymerase inhibitor, has been approved by Food and Drug Administration and European commission for the treatment of ovarian cancer with any *BRCA1/2* mutations. The first case of a *BRCA1*-mutated GBC patient responded to olaparib treatment is reported here.

**Key words:** *BRCA*; Mutation; Olaparib; poly ADP-ribose polymerase inhibitor; Gallbladder cancer

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**Core tip:** Gallbladder cancer (GBC) is the most common neoplasm of the biliary tract system. *BRCA1*, the first major breast cancer susceptibility gene, has been widely studied in breast and ovarian cancers. Olaparib, an oral poly ADP-ribose polymerase (PARP) inhibitor, has been approved by FDA and European commission for the treatment of ovarian cancer with any *BRCA1/2* mutations. However, there is no report of germline *BRCA1* functional mutation in GBC prior to this case. Even further the GBC with *BRCA1* mutation responded to PARP inhibitor olaparib.

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**INTRODUCTION**

Gallbladder cancer (GBC) derives from the mucosal epithelial lining of the gallbladder and the cystic duct. It is a relatively rare malignancy but the most frequent malignant neoplasm of the biliary tract system. Epidemiological studies have demonstrated that the incidence of GBC is characterized by remarkable geographic distribution and ethnic disparities. The incidence is extraordinarily high in American Indians, elevated in Southeast Asia and quite low elsewhere in the Americas[1]. Although GBC limits in Southeast Asia, with increasing global migration, the incidence is also increasing in the west, and spreads worldwide. The prognosis of GBC is dismal and the median survival for locally advanced GBC with non-surgically treatment is about 8 mo[2]. Some patients detected incidentally during routine cholecystectomy for cholelithiasis have a long-term survival, but they only account for 2% of all cases with GBC[3]. Clinically, the adjuvant treatment for GBC is gemcitabine or 5-fluorouracil (5-FU)-based chemotherapy, with or without radiotherapy[4]. Even though response rate remains low, there is no effective treatment. Here we reported that a *BRCA1*-mutated GBC patient responded to poly ADP-ribose polymerase inhibitor (PARPi) olaparib.

**CASE REPORT**

A 74-year-old man, with a past history of primary hypertension, atrial fibrillation, coronary disease and cholelithiasis, presented with epigastric pain. The patient underwent a robot-assisted prostate cancer surgery on November 29, 2013 and his mother had died of esophageal cancer. Computed tomography (CT) of the abdomen revealed multiple low-density intrahepatic lesions besides gallbladder on May 7, 2015. PET-CT revealed multiple hypermetabolic intrahepatic lesions apart from porta hepatis on May 14, 2015. A laparoscopic exploration was performed and an intrahepatic biopsy was conducted on May 26, 2015. Histologic examination indicated GBC (Figure 1). Considering the dismal prognosis and his poor physical conditions, systemic chemotherapy was not preferred. After obtained consent from the patient and his family, we tested the tissue. Two specimens from different liver metastases and blood sample have been sent for next generation sequencing panel. We detected all genomic alteration types on over 390 genes commonly associated with cancers and found a somatic *MET* P1086A mutation in one of two liver metastases. But there was no literature to confirm this was a functional mutation. Bioinformatics analysis also suspected *MET* P1086A could have impact on MET function. However, we also detected a germinal *BRCA1* Q858\* mutation in both liver metastases and further Sanger sequencing confirmed this result (Figure 2). Furthermore, the patient’s offspring and siblings also had been done for *BRCA* mutation screening from their saliva samples and some family members were also *BRCA1* Q858\* mutation carriers (Figure 3). The nonsense mutation may lead to the premature termination of BRCA1 protein translation and nonsense-mediated mRNA decay (NMD), and the loss-of-function disenables its involvement in transcriptional regulation of gene expression and repair of DNA damage, particularly double-strand breaks[5]. Several studies have demonstrated that *BRCA1* mutations increase the risks of breast, ovarian, prostate and pancreatic cancer[5-7]. Poly ADP-ribose polymerase (PARP) inhibitors have been studies as potential cancer therapeutics by inhibiting base excision repair as well as trapping PARP[8,9]. A number of clinical trials have shown patients with germline *BRCA1/2* mutation, especially in breast and ovarian cancer to PARP inhibitor olaparib with survival benefit[10-12]. Based on the gene alteration testing report and the clinical trial studies, the patient was started on olaparib 400 mg twice daily on July 21, 2015 (Figure 4). The patient can tolerate the dose and subsequently his pain was relieved significantly. On August 23, 2015, CT of the abdomen revealed the shrinkage of both intra and extra hepatic lesions and even some extra hepatic lesions appeared to be invisible (Figure 5). The patient responded well to olaparib until the occurrence of obstructive jaundice. On October 9, 2015, CT of the abdomen indicated that intrahepatic lesions dwindled, nevertheless, extrahepatic lesions became large and progressed (Figure 6). Subsequently, a PTCD was performed to reduce the serum bilirubin level and the olaparib treatment was suspended since then. We intended to resume olaparib treatment in combination with platinum agents after some while. Unfortunately, the patient passed away as a result of severe biliary tract infection on November 25, 2015.

**DISCUSSION**

Like other cancers, substantial molecular alterations in genes contribute to the pathogenesis of GBC. Hitherto, in the GBC, over 1450 single nucleotide variants (SNV), 34 deletions have been reported. The most frequent mutations are *TP53* (18%-63%), *KRAS*, *ERRB3* and *ERBB2* (*HER2*)[13]. *BRCA1*, the first major breast cancer susceptibility gene, has been widely studied in breast and ovarian cancers. However, there is no report of germline *BRCA1* functional mutation in GBC prior to this case. Even further the GBC with *BRCA1* mutation responded to PARP inhibitor olaparib.

Association of *BRCA1/2* mutations with susceptibility to breast and ovarian cancer has been investigated for years. It is estimated that about 60% of women with *BRCA1/2* mutations have developed breast cancer[14]. A woman, who carries a germline *BRCA1/2* mutation could be 5 times more likely to develop breast cancer than the one, who does not carry any BRCA1/2 mutation[15]. Men who have *BRCA1/2* mutations are more likely to have prostate or pancreatic cancers. Men are 3.5 times and 8.6 times more likely to develop prostate cancer for *BRCA1* and *BRCA2* mutation carriers by age 65, respectively[16]. Similar to prostate cancer, *BRCA1/2* poses a risk of pancreatic cancer development. Overall, *BRCA1* mutation increases the risk by 0- to 4.11-fold, while the *BRCA2* mutation increases the risk by 2.13- to 21.7-fold[17].

The BRCA proteins play a pivotal role in repair of double-strand DNA breaks (DSB) *via* homologous recombination (HR). Due to deficiency in BRCA proteins, *BRCA*-mutated cells are not capable of locating the DNA recombinase RAD51 to damaged DNA and hence are unable to perform HR efficiently. Subsequently, an error-prone DNA repair mechanism, such as nonhomologous end joining (NHEJ), is compelled to use by cells, which often leads to cell death. Base excision repair (BER), as one of single strand DNA break (SSB) repair mechanism, is crucial to address damaged single strand DNA. Olaparib is an oral PARPi, and it has been approved by FDA and European commission for the treatment of ovarian cancer with any *BRCA1/2* mutations in 2014. Olaparib, by means of blocking base excision repair, can convert single-strand DNA breaks to double-strand breaks, which gives rise to selective death of HR-deficient tumor cells. Mounting Evidence has indicated that *BRCA*-mutated cancers are highly sensitive to PARP inhibitors and platinum agents. Compared with wild-type cells, *BRCA*-mutated cells are 1000-fold and 5-fold more sensitive to PARPi and platinum agents respectively[18,19].

In this case, we observed that the intrahepatic lesions had a favourable response to olaparib, while the extrahepatic lesions had a progression with the emergence of olaparib resistance. Despite olaparib holds considerable promise in targeted therapies for *BRCA*-mutated breast or ovarian cancers, drug resistance has became of a potential issue. As far, several resistance mechanisms have been proposed. Olaparib-triggered, secondary *BRCA* mutations are perhaps considered as the most well-validated mechanism in patients, others include up-regulation of PgP transporter, loss of 53BP1 as well as PARP expression[20-22]. The comprehensive genomic alteration testing may provide novel clinical strategies for personalized therapy in advanced GBC. More mechanisms for the chemoresistance are expected to explore and understand in the future, which will help re-sensitize tumor cells to PARPi and improve the long-term effectiveness.

**COMMENTS**

***Case characteristics***

A 74-year-old man, with a past history of primary hypertension, atrial fibrillation, coronary disease and cholelithiasis, presented with epigastric pain.

***Clinical diagnosis***

The physical examination revealed tenderness of the epigastrium, without rebound tenderness and muscle tonus.

***Differential diagnosis***

Hepatocellular carcinoma, intrahepatic cholangiocarcinoma, metastatic lesions of non-hepatic origins, gallbladder cancer.

***Laboratory diagnosis***

The blood test for tumor markers revealed elevation of carbohydrate antigen (CA) 19-9 (4815.0 U/mL) and carcinoembryonic antigen (CEA) (12.5 ng/mL), while alpha-fetoprotein (AFP) and prostate specific antigen (PSA) were within normal limits. The blood test for liver function revealed elevation of total bilirubin (TBil) (23.0 μmol/L)and direct bilirubin (DBil) (9.2 μmol/L), while alanine aminotransferase (ALT) was within normal limit and the test for hepatitis virus was negative.

***Imaging diagnosi*s**

Computed tomography (CT) revealed multiple low-density intrahepatic lesions besides gallbladder. Positron emission tomography–CT (PET-CT) revealed multiple hypermetabolic intrahepatic lesions apart from porta hepatis.

***Pathological diagnosis***

Pathological examination revealed gallbladder cancer with hepatic infiltration.

***Treatment***

The patient underwent a laparoscopic exploration and an intrahepatic biopsy. Two specimens from different liver metastases and blood sample had been sent for next generation sequencing panel. A germinal *BRCA1* Q858\* mutation in both liver metastases had been detected and further Sanger sequencing confirmed this result. Based on the gene alteration testing report and the clinical trial studies, the patient was started on olaparib 400 mg twice daily.

***Related reports***

There is no report of germline *BRCA1* functional mutation in gallbladder cancer prior to this case. Even further the gallbladder cancer with *BRCA1* mutation responded to PARP inhibitor olaparib.

***Term explanation***

*BRCA1*, the first major breast cancer susceptibility gene, has been widely studied in breast and ovarian cancers, their mutation carriers are at a high risk for cancer development. Olaparib, an oral poly ADP-ribose polymerase (PARP) inhibitor, has been approved by FDA and European commission for the treatment of ovarian cancer with any *BRCA1/2* mutations.

***Experiences and lessons***

This case report describes the response of a germline *BRCA1*-mutated gallbladder cancer patient to poly ADP-ribose polymerase inhibitor (PARPi) olaparib. While the comprehensive genomic alteration testing may provide novel clinical strategies for personalized therapy in advanced gallbladder cancer, drug resistance has become of a potential issue. More discoveries concerning the mechanisms for chemoresistance will help re-sensitize tumor cells to PARPi and improve the long-term effectiveness.

***Peer-review***

This is a very interesting case report. In this manuscript, the authors reported a 74-year-old man, with a past history of primary hypertension, atrial fibrillation, coronary disease and cholelithiasis, presented with epigastric pain.

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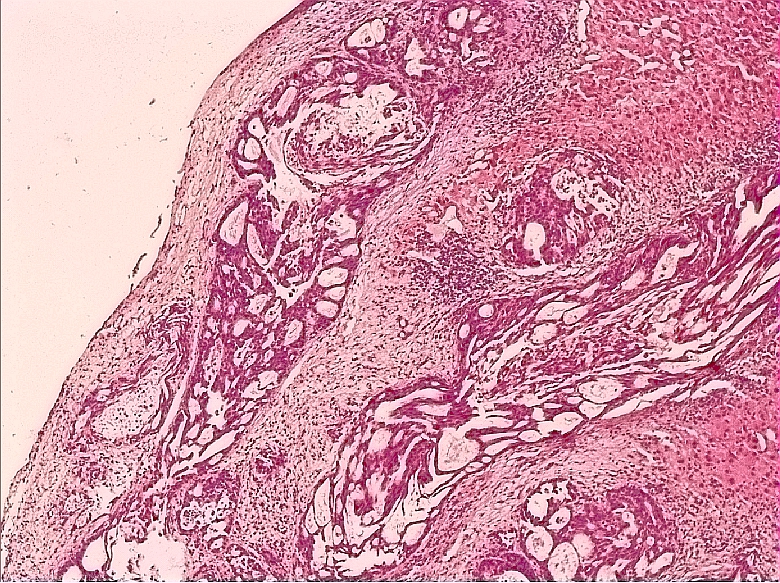
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Grade B (Very good): b, b, b

Grade C (Good): 0

Grade D (Fair): 0

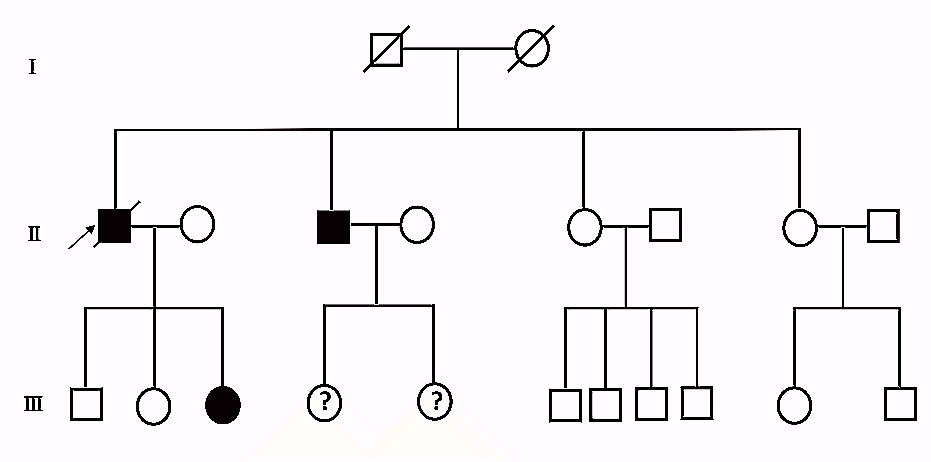
Grade E (Poor): 0



**Figure 1 Histologic examination indicated gallbladder cancer with hepatic infiltration.**

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**Figure 2 Genomic images from the integrated genome viewer for the alteration in *BRCA1* found in the patient’s blood sample.** The number of reads for the reference allele and variant allele are shown for each alteration.



**Figure 3** **Pedigree of 74-year-old man affected by gallbladder cancer found to be carrier of *BRCA1* gene mutation (indicated with arrow).** Black denotes carrier of *BRCA1* mutation.

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**Figure 4** **baseline (July 21, 2015) computed tomography of the abdomen revealed many intra and extra hepatic lesions when to initiate olaparib treatment.**

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**Figure 5 One month post-olaparib treatment (August 23, 2015).** computed tomography of the abdomen revealed the shrinkage in both intra and extra hepatic lesions and even extra hepatic lesions appeared to be invisible.

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**Figure 6** **Two and half months post-olaparib treatment (October 9,2015).** computed tomography of the abdomen indicated that intrahepatic lesions dwindled, nevertheless, extrahepatic lesions became large and progressed.