Durable response to olaparib in pancreatic duct adenocarcinoma with deleterious ARID1A mutation

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To the Editor: Pancreatic cancer is one of the leading causes of cancer death worldwide. The significant symptoms prompting diagnosis often appear once the tumor invades surrounding tissues or metastasizes, resulting in the late diagnosis and the infeasibility of complete resection. For the patients at advanced stage, the shortage of efficient medication for systemic therapy further limited their survival time. Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi), possesses several documented mechanisms of action, including the inhibition of base excision repair as well as trapping of PARP.[1] These mechanisms inhibit the repair of single-stranded break (SSB) and therefore lead to the induction of double-stranded break (DSB). Tumors with severe defect in homologous recombination-DNA damage repair (HR-DDR) are ineffective in repair of DSB, which is theoretically susceptible to PARPi therapy. ARID1A, a part of the large ATP-dependent chromatin remodeling complex SNF/SWI, is required for transcriptional activation of genes normally repressed by chromatin. Both truncating mutation and loss of copy number may lead to the shortage of functional ARID1A protein, causing HR-DRR deficiency that associates with the response to PARPi. Preclinical studies showed the loss of ARID1A may sensitize cancer cells to PARPi.[2] However, no relevant trial or case report of pancreatic ductal adenocarcinoma (PDAC) was published to date. Here we present the report of a PDAC patient with deleterious ARID1A mutation (p.Q1327*) who remained response to olaparib-based therapy for more than 13.0 months.

A 50-year-old male presented to hospital due to a 1-month history of dull pain in lumbar and abdominal area, without jaundice, tea-colored urine, or acholic stools. The patient did not have a personal history of cancer, but his elder sister was attacked by breast cancer at the age of 53. Measurement of serum tumor biomarkers revealed an abnormal value of carbohydrate antigen 19-9 (CA 19-9, 334.10 U/mL). An enhanced MRI elucidated a 3.0 cm × 3.4 cm mass in the body-tail junction of pancreas [Figure 1A]. Positron emission tomography (PET) showed the maximum standard uptake value of the mass was 4.8, and as PET suggested, the lesion was likely to be cancerous. Fine-needle aspiration was rejected by the patient.

Surgical exploration was performed. Based on the intraoperative findings including an approximately 2.0 cm × 1.5 cm mass at the body-tail junction of pancreas and an invasion of splenic vein, a distal pancreatectomy with splenic resection was performed [Figure 1B]. Pathological assessment indicated a well-differentiated PDAC [Figure 1C and 1D] with negative margin, and only 1 (out of 11) positive lymph node. The pathological stage was determined as stage IIb (T1N1M0).

After the resection, six cycles of gemcitabine plus S-1 (gemcitabine 800 mg m$^{-2}$·d$^{-1}$, d1-d7 q3w; S-1 60 mg m$^{-2}$·d$^{-1}$, d1-d14 q3w) as adjuvant therapy were administrated (the patient refused to receive FOLFIRINOX as the National Comprehensive Cancer Network [NCCN] guideline suggested), the CA 19-9 level dropped to 21.85 U/mL. However, the MRI scan at 2 months after the chemotherapy revealed a new lesion of the lymph node behind the resection margin of the pancreas, with a maximum diameter of 1.3 cm (Figure 1E), and the CA 19-9 level rose to 77.31 U/mL, suggesting the lesion could be a cancerous one.

After a weekly multidisciplinary team (MDT) discussion, considering the possible insufficient dissection of minimal lymph node and gemcitabine plus S-1 failure to stop its progression, we try to seek further treatment. The specimens from surgical resection underwent genomic assessments including targeted sequencing of cancer-related genes and polymerase chain reaction (PCR) to detect microsatellite instability. In total, four somatic

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mutations were identified: ARID1A (c.3979C>T, p.Q1327∗), KRAS (c.43G>C, p.G12R), TP53 (c.817C>T, p.R273C), and CBL (c.1388C>T, p.A463V). The microsatellites including BAT-25, BAT-26, NR-21, NR-24, and MONO-27 were all stable (microsatellite stable, MSS). Despite no targeted chemicals were approved for cancer patients harboring deleterious ARID1A mutation, PARPi might be efficacious on account of the HR-DDR defect induced by the loss of functional ARID1A protein.

Olaparib, an oral PARP inhibitor, have been adopted as monotherapy for 6 months (300 mg, twice a day), and the patient have shown relatively well tolerance to olaparib during this period, no dose decreasing or treatment interruption occurred. The MRI scan revealed an objective response that the maximum diameter of the lesion reduced by 40% to 0.6 cm [Figure 1F]. To determine whether this patient was risky of recurrence, liquid biopsy of circulating tumor DNA was executed and all of the four somatic mutations were undetectable in the blood sample. In view of this result, it is plausible that at most limited progression occurred. Thus, the treatment of olaparib continued with an elevated dose of 400 mg twice a day. The patient remains under follow-up and the progression-free survival (PFS) of olaparib therapy reached 13.0 months (as of July 21, 2019).

Figure 1: (A) Magnetic Resonance Imaging (MRI) scan before surgical resection, the red arrow indicates the primary tumor in pancreas. (B) A baseline MRI scan after surgical resection, no recurrent lesions were found. (C) Hematoxylin and eosin stain of the specimen from surgical resection (original magnification × 40). (D) Hematoxylin and eosin stain of the specimen from surgical resection (original magnification × 200). (E) MRI scan after adjuvant therapy, a new lesion within a lymph node marked by a red arrow. (F) MRI scan after 6 months of olaparib, which suggested a shrinkage of the lesion.
To date, olaparib have been approved for breast and ovarian cancers harboring deleterious or suspected-deleterious germline BRCA1/2 mutations (gBRCAm). In addition, a basket trial in gBRCAm-associated breast, ovarian, prostate and pancreatic cancers, revealed a response rate at 21.7% in recurrent PDAC patients, indicating the efficacy of PARPi in HR-defective PDAC. As a second- or later-line regimen in BRCA-mutated PDAC patients, veliparib displayed limited antitumor activity (objective response rate [ORR], 0 [0/16]), while olaparib (ORR, 21.7% [5/23]) delivered moderate benefit, and in a recently published phase 3 trial, olaparib maintenance group showed significant longer median progression-free survival than the placebo (7.4 months vs. 3.8 months; hazard ratio for disease progression or death [HR], 53%). Besides BRCA1/2, other genes related to HR-DDR were discovered to be associated with the response to olaparib in prostate carcinomas, including ATM, PALB2, CHEK2, FANCA, or HDAC2. Similarly, a preclinical study revealed responses to olaparib in ATM-mutated PDAC cell lines, both in vitro and in vivo, indicating the potential of acquiring benefit from olaparib in HR-deficient PDAC patients, including but not limited to the BRCA1/2-mutated population. In this case, a nonsense mutation (c.3979C>T, p.Q1327*) occurred, plausibly resulting in loss of ARID1A expression via nonsense-mediated mRNA decay or truncating ARID1A protein that lacks SNF/SWI-like complex subunit. Both consequences might induce the malfunction of ARID1A and the defect in repairing DSB, contributing to the objective response observed in this patient.

This is the report of a PDAC patient harboring a deleterious mutation in ARID1A, who obtained a long-term response to olaparib-based therapy in China. This case highlights the importance of NGS testing in PDAC treatment, and indicates the potential efficacy of PARPi in HR-deficient PDAC patients, besides the gBRCAm population. Further investigation is warranted to confirm the efficacy of this treatment with larger sample size.

**Declaration of patient consent**

All participants provided their written informed consent before participating in the study. In the forms, all patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

None.

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