Response of germline BRCA2-mutated advanced pancreatic acinar cell carcinoma to olaparib
A case report

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Abstract
Rationale: Pancreatic acinar cell carcinoma (PACC) is a relatively rare malignancy of the exocrine pancreas. BRCA2, a cancer susceptibility gene, has been widely studied in breast and ovarian carcinomas as mutation carriers for this gene are at a high risk for cancer development. Olaparib, an oral poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, has been approved for the treatment of ovarian cancer with any BRCA 1/2 mutations. Herein, we report the first case of a germline BRCA2-mutated unresectable advanced PACC patient who responded well to olaparib treatment.

Patient concerns: A 59-year-old male with a family history of cancer presented with a persistent epigastric dull pain for 3 months.

Diagnosis: The patient was diagnosed with advanced PACC based on computed tomography (CT) scan, laparotomy, and pathology.

Interventions: Exploratory laparotomy, intratumoral brachytherapy by radioiodine-125 seeds, modified FOLFIRINOX chemotherapy, and targeted therapy with olaparib were administered.

Outcomes: The patient responded well to olaparib until the occurrence of severe adverse drug reactions, he died as a result of multiple organ failure with an overall survival period of 12 months.

Lessons: As a PARP inhibitor, olaparib has remarkable curative effect not only on breast and ovarian cancers, but also on other malignancies with BRCA mutations. Patients with advanced cancer could benefit from active targeted therapy with improvement in overall survival and quality of life.

Abbreviations: AFP = alpha-fetoprotein, AJCC = American Joint Committee on Cancer, and End Results data, BER = base excision repair, CA19-9 = carbohydrate antigen 19-9, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, Epidemiology, FDA = Food and Drug Administration, HR = homologous recombination, JPS = Pancreatic Cancer Registry of the Japan Pancreas Society, MDT = multidisciplinary team, MST = median survival time, NET = neuroendocrine tumor, NGS = next generation sequencing, PACC = pancreatic acinar cell carcinoma, PARP = poly(adenosine diphosphate-ribose) polymerase, PD = progressive disease, PDAC = pancreatic ductal adenocarcinoma, PR = partial response, SEER = surveillance.

Keywords: BRCA2-mutation, modified FOLFIRINOX, olaparib, pancreatic acinar cell carcinoma, poly(adenosine diphosphate-ribose) polymerase inhibitor, radioiodine-125

1. Introduction
Pancreatic acinar cell carcinoma (PACC), a relatively rare malignancy of the exocrine pancreas, accounts for <1% of primary pancreatic neoplasms, compared with pancreatic ductal adenocarcinoma (PDAC).[1-4] Patients with PACC are generally asymptomatic but may experience abdominal pain and jaundice albeit less frequently than those with PDACs.[5] Kim et al have suggested that that Schmid syndrome which includes symptoms such as adiponecrosis, polyarthritis, and eosinophilia may be clinical manifestations associated with PACCs; however, research on this is limited because of the low incidence.[2,6] In some cases and unlike PDAC, alpha-fetoprotein (AFP) may be abnormally elevated instead of carbohydrate antigen 19-9 (CA19-9).[7] The radiological differential diagnosis of PACC includes PDAC, neuroendocrine tumors (NET), solid pseudopapillary tumors, pancreatic blastomas, mutinous cystic neoplasms, and pseudocysts. Computed tomography (CT) is often not useful for diagnosis; however, characteristics of the tumor can be seen. On CT, PACCs are often sizable, hypodense pancreatic masses with a density intermediate to that of PDACs and pancreatic NETs, which are more hypodense and hyperdense, respectively.[8] When definitively diagnosed, half of the patients with PACC have large primary tumors with distant metastases; however, population-based retrospective analysis of Surveillance, Epidemiology, and End Results data (SEER) and Pancreatic Cancer Registry of the Japan Pancreas Society (JPS) demonstrated higher rates of 5-year survival in PACCs compared with that in PDACs for both resected and unresected cases.[4,9] According to the present reports, the 5-year survival rate for the resected cases was
43.9\% to 71.6\%, with a median survival time (MST) of 12 to 123 months and a 5-year survival rate for unresected cases was 0\% to 22\%, with an MST of 3 to 25 months. \[4,9–15\] For unresectable PACCs, chemotherapy and radiotherapy are other therapeutic options, but insufficient research has accumulated on the efficacy of chemotherapy, and no reports have described radiotherapy alone. Moreover, there have been limited studies or reports on relevant targeted drugs.

Here a unique case of advanced PACC with germline BRCA2-mutation, progression of disease after radioiodine-125 and chemoradiotherapy, further treatment with the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor-olaparib is presented and clinical features and therapeutic efficacy are discussed. Informed written consent was obtained from the patient’s family member for sharing and publication of this case and accompanying images.

### 2. Case description

A 59-year-old Chinese male patient, anamnesis of hepatitis A for 10 years, without history of vomiting and diarrhea was hospitalized after 3 months of persistent epigastric dull pain, which could be relieved while maintaining a left recumbent position. The patient had a family history of cancer—his father...
died from lung cancer, and his mother and brother had hepatic carcinoma. No abnormalities were found on admission during the physical examinations and a routine blood biochemical examination was normal. Enhanced CT of the abdomen revealed a large mass in the tail of the pancreas with ill-defined margins, 7.1 × 5.8 cm in size, invading the celiac axis, spleen vessels, splenic hilum and left adrenal gland with retroperitoneal lymph nodes metastases which exhibited uneven density lower than that of the pancreatic parenchyma on February 23, 2017 (Fig. 1). Further examination of serum tumor biomarkers revealed that CA19-9 was in the normal range of 6.08 U/mL, but AFP was elevated to an abnormally high level of 89.39 ng/mL. With written informed consent, an exploratory laparotomy was performed on February 24, 2017. Due to intraoperative findings that indicated no metastasis, as found on CT, the patient underwent a pancreatic biopsy and intratumoral brachytherapy by radioiodine-125 seeds. With histopathological and immunohistochemical examinations the patient was diagnosed with PACC and classified as stage III (T4NxM0) according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging for pancreatic cancer. The postoperative recovery was uneventful without complications and the epigastric pain was relieved obviously. However, CT reexamination indicated that the metastatic lymph nodes lesion increased. Subsequently, the patient was transferred to the department of abdominal oncology. After a multidisciplinary team (MDT) discussion, combined with the Eastern Cooperative Oncology Group (ECOG) performance score of 1 point, 3 cycles of modified FOLFIRINOX (mFOLFIRINOX) chemotherapy (a 2-h intravenous infusion of oxaliplatin 65 mg/m², followed by another 2-
intravenous infusion of leucovorin 400 mg/m², concomitantly with an additional 1.5-hour intravenous infusion of irinotecan 135 mg/m², and a subsequent intravenous infusion of fluorouracil 2400 mg/m² over 46 hours every 2 weeks) were administered from March 22 to May 19. After 2 cycles of chemotherapy, the primary lesion of the pancreas was classified as stable disease (SD), but the retroperitoneal lymph nodes enlarged 34.1% than before which impelled us to combine the third cycle of chemotherapy with metastatic lymph node palliative radiotherapy. On July 20, CT reexamination revealed progressive enlargement of lymph nodes and new metastases in the liver (Fig. 2); meanwhile, the AFP had soared to 450.1 ng/mL and the overall efficacy was evaluated for progressive disease (PD). At the patient’s request, intratumoral brachytherapy by radioiodine-125 was performed again. Surgical exploration and intraoperative ultrasonography definitely confirmed multiple hepatic and mesenteric metastases, which meant that tumor stage has progressed to stage IV (T4NxM1). To actively seek further treatment and after obtaining consent from the patient and his family, 2 specimens from the hepatic metastases and primary tumor as well as a blood sample were sent for a next generation sequencing (NGS) panel. This process detected all genomic alteration types of over 390 genes commonly associated with malignancies; somatic SMAD4, CTNNB1, KEAP1 mutations were found but no effective target drugs for these biomarkers were approved by the Food and Drug Administration (FDA) currently. However, a germline BRCA2 p.I332Nfs*4 heterozygous mutation was detected in both metastases and primary lesion and further Sanger sequencing confirmed this result. Olaparib, an oral PARP inhibitor, has promising antitumor activity.
activity in patients with metastatic breast cancer and a germline BRCA mutation, even in patients with PDAC and a BRCA mutation. Therefore, with cooperation of the family members, the trial of olaparib was administered from August 12 to September 18 at a dose of 400mg twice a day. CT imaging indicated the shrinkage of both intra- and extrahepatic lesions (30.57% reduced compared to that seen in the July 20th imaging results) and some intra-hepatic lesions even appeared to be invisible (Fig. 3). Furthermore, the AFP level declined to 174ng/mL. The patient responded well to olaparib until severe adverse drug reactions occurred including myelosuppression, asthenia, and abdominal pain, which led to a reduction in the dose to 200 mg twice a day from September 19 to October 20. A CT on October 20 suggested a 10.45% increase in metastatic lymph nodes and liver metastases compared with the previous imaging (Fig. 4). In summary, the overall efficacy of olaparib treatment was evaluated for partial response (PR). Unfortunately, due to the serious adverse drug reactions, voluntary reduction or even withdrawal of the drug frequently occurred, resulting in disease progression. The patient passed away as a result of multiple organ failure in March 2018 with an overall survival period of 12 months.

3. Discussion and conclusion
Like other cancers, substantial molecular alterations in genes contribute to the pathogenesis of PACC which is a rare malignancy representing <1% of all pancreatic malignancies. Unlike PDACs, genomic alterations in KARS, SMAD4, CDKN2A, and TP53 genes were observed in PACCs but less frequently. Other mutations noted in PACCs were in BRCA1, BRCA2, RB1, BRAF/RAF1, ATM, GNAS, FAT, MEN1, and JAK1 genes, along with mutations in the WNT-β-catenin pathway (APC and CTNN1 genes). Among these, the BRCA2 mutation, the major breast cancer susceptibility gene, has been widely studied in breast and ovarian cancers, and accounts for 4% to 43% in relevant research. A woman who carries a germline BRCA2 mutation could be 5 times more likely to have breast cancer than one who does not carry the mutation. Similarly, men who have the BRCA2 mutations are 8.6 times more likely to develop a prostate malignancy and 2.13- to 21.7-fold more likely to develop pancreatic carcinoma. The BRCA proteins play a pivotal role in the repair of double-strand DNA breaks via homologous recombination (HR). Due to a deficiency in BRCA proteins, BRCA-mutated cells are not capable of locating the DNA recombinase RAD51 due to damaged DNA and hence are unable to perform HR efficiently. Subsequently, an error-prone DNA repair mechanism, such as nonhomologous end joining, is compelled to be used by cells, which often leads to cell death. Because of the lack of DNA double-strand break repair by homologous recombination, mutations in BRCA genes, which are tumor-suppressor genes, the patient is predisposed to multiple cancers. The PARP family of enzymes are central to the repair of DNA single-strand breaks through base excision repair (BER), one of the single-strand DNA break repair mechanisms crucial to addressing damaged single-strand DNA. In vitro experiments showed how BRCA-mutated cells are sensitive to PARP inhibition, due to the
synthetic lethality that results from unresolved DNA damage and the replication arrest from physical obstruction of replication forks by PARP trapping and other mechanisms.[29,30]

Olaparib, an oral PARP inhibitor, was approved by the FDA and European Commission for the treatment of ovarian cancer with any BRCA1/2 mutations in 2014. By means of blocking BER, olaparib 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 PARP inhibitor and platinum agents, respectively. In addition to breast, ovarian and prostate cancer, there have been previous reports on the use of olaparib in the treatment of PDAC and gallbladder cancer.[17,31] However, there is no report of PACC with a BRCA2 mutation that responded to the PARP inhibitor-olaparib before this case.

In this report, we present a rare case of unresectable advanced PACC, within the celiac axis, treated with intratumoral brachytherapy by radiiodine-125, lymph node radiotherapy and adjuvant mFOLIRINOX chemotherapy which has been the first-line chemotherapy regimen for pancreatic cancer. The primary lesion had a favorable response, whereas the lymph nodes had a progression, followed by hepatic metastases. To our surprise, active use of olaparib, the targeted drug for BRCA mutations, significantly controlled the intrapancreatic and extrapancreatic lesions, and even after dose reduction, the efficacy was noted for PR. Simultaneously, the level of AFP was also positively correlated with the development of the disease. For this patient, drug withdrawal caused by serious side effects of olaparib was the direct factor implicated disease progression. If the adverse reactions of targeted drugs can be effectively managed and dosages maintained or reduced as appropriate, the overall survival period may be further extended. For advanced PACC, chemotherapy for PDAC have demonstrated therapeutic effectiveness and radiiodine-125 may also be effective. With the development and popularization of NGS, exploring new targeted drugs to help treat unresectable advanced PACC or even PDAC with poor prognosis are needed. Olaparib, as a PARP inhibitor, has remarkable curative effects not only on breast and ovarian cancers, but may also have this effect on other malignancies with BRCA mutations.

In summary, patients with advanced cancer could benefit from active targeted therapy with improvement in overall survival and quality of life. More trials regarding molecular targeted therapy are expected to be conducted in the future. At the same time, further in-depth research in relation to strategies for reducing the side effects of olaparib, neoadjuvant chemotherapy applying PARP inhibitors and combinations of targeted drugs and traditional chemotherapy are needed.

**Author contributions**

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