Case Report

Successful treatment of GEMOX regimen combined with nimotuzumab in the pancreatic cancer with wild KRAS and mutant BRCA: a report of two cases

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Background: Pancreatic cancer is characterized by chemoresistance. In recent years, more potential therapeutic molecular targets for pancreatic cancer have been developed, and thus increasing attention has been paid to precise chemotherapy to improve the prognosis of patients with advanced pancreatic cancer.

Case Description: In this study, we reported two rare cases of advanced pancreatic cancer. One patient was diagnosed with retroperitoneal lymph node metastasis after radical resection of pancreatic ductal adenocarcinoma. The diagnosis of another patient was pancreatic ductal adenocarcinoma with liver metastasis. The whole genome sequencing of their tumor tissues detected both wild-type Kirsten rat sarcoma viral oncogene homolog (KRAS) and mutant breast cancer susceptibility gene (BRCA). And immunohistochemistry showed their tumor tissue was negative for epidermal growth factor receptor. We used the combined chemotherapy of gemcitabine (1,000 mg/m^2) + oxaliplatin (135 mg/m^2) + nimotuzumab (400 mg). After nine times of chemotherapy, the imaging examinations including positron emission tomography-computed tomography showed that both cases achieved complete remission. And there were no serious side effects during chemotherapy. Then, the patients were treated with oral olaparide (600 mg/day) for one year, and survived without tumor progress for more than 1.5 years.

Conclusions: These two cases achieved excellent effects of precise chemotherapy, which provided an important reference for the treatment of pancreatic cancer patients with wild KRAS and mutant BRCA.

Keywords: Pancreatic cancer; Kirsten rat sarcoma viral oncogene homolog (KRAS); breast cancer susceptibility gene (BRCA); chemotherapy; case report

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Introduction

Pancreatic cancer is one of the most common gastrointestinal malignancies in the world, with high malignancy and poor prognosis, and its 5-year survival rate is about 13% (1). Radical resection is the only way to cure pancreatic cancer. Only 10–20% of patients diagnosed with localized pancreatic cancer have the chance to undergo radical surgery, and the

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recurrence rate within 2 years after radical surgery is as high as 80% (2,3). The main treatment for patients with advanced pancreatic cancer is systemic chemotherapy, which prolongs the progression-free survival (PFS) and overall survival (OS) of patients, and improves their quality of life. At present, the first-line chemotherapy regimen recommended by international guidelines is FOLFIRINOX regimen (irinotecan + fluorouracil + calcium folinate + oxaliplatin) or AG regimen (gemcitabine + albumin bound paclitaxel). However, the objective effective rates of both regimens are about 30%, and the PFS is about 6 months, which is still unsatisfactory (4). The gene detection technology provides the feasibility of precise treatment in a variety of malignant tumors including pancreatic cancer (5). Currently, the precise therapy based on gene detection in pancreatic cancer is still in the exploratory stage (6). Here, we first report two patients with advanced pancreatic cancer who were successfully treated with precise chemotherapy of gemcitabine + oxaliplatin + nimotuzumab based on specific gene type wild-type Kirsten rat sarcoma viral oncogene homolog (KRAS) and mutant breast cancer susceptibility gene (BRCA). We present the following cases in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-68/rc).

Case presentation

Case 1, a 58-year-old man, was hospitalized due to the recurrence of pancreatic cancer 8 months after radical surgery. He has no history of hepatitis, hypertension, diabetes and heart disease, and no family history of malignant tumors. The patient underwent radical pancreaticoduodenectomy for pancreatic head cancer 8 months ago. Postoperative pathology showed pancreatic ductal adenocarcinoma (grade II–III) with tumor thrombus in the vessels, nerve invasion and peripancreatic tissue invasion. One peripancreatic lymph node (1/5) was found with cancer metastasis, and no peri-coeliac artery lymph nodes were found with metastasis [pathological TNM stage (pTNM) IIB, according to 8th edition of the American Joint Committee on Cancer (AJCC) staging system]. Then, the patient was treated with adjuvant chemotherapy using gemcitabine combined with albumin paclitaxel once every three weeks for six times. In follow-up of 8 months after operation, the upper abdominal enhanced computed tomography (CT) showed that the lymph node behind the proximal superior mesenteric artery was enlarged and was considered as tumor metastasis (*Figure 1A*). And positron emission tomography-computed tomography (PET-CT) also showed that a soft tissue nodule with increased fluorodeoxyglucose (FDG) metabolism located at the same site, which was considered as tumor metastasis (*Figure 1B*). The results of blood routine test and liver and kidney function test were normal, and the tumor markers [alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA)199, CA125] were also in the normal range. He was diagnosed with advanced pancreatic adenocarcinoma [clinical TNM stage (cTNM) IV, according to 8th edition of the AJCC staging system]. The whole genome sequencing detected somatic BRCA2 mutation and wild-type KRAS in the radically resected tumor tissues. Immunohistochemistry showed the tumor tissue was negative for epidermal growth factor receptor (EGFR). Based on previous studies, we chose the chemotherapy regimen of gemcitabine (1,000 mg/m^2) + oxaliplatin (135 mg/m^2) + nimotuzumab 400 mg (21 days as one cycle, once at 1-, 8-, 15-day) (7,8). After two cycles of chemotherapy, the upper abdominal enhanced magnetic resonance imaging (MRI) showed that the metastatic lymph node was obviously shrinked (*Figure 1C*). After three cycles of chemotherapy, the metastatic nodule was not observed in the PET-CT (*Figure 1D*). After neurotrophic therapy of mecobalamin, VitB1 and VitB12, the patient's limb numbness induced by chemotherapy was significantly alleviated. Then, the patient was treated with olaparide (600 mg/day) for one year. The patient has survived for

Highlight box

Key findings

- This is the first report of advanced pancreatic cancer with wild Kirsten rat sarcoma viral oncogene homolog (KRAS) and mutant breast cancer susceptibility gene (BRCA) to be treated with chemotherapy of gemcitabine + oxaliplatin + nimotuzumab in the first line setting.

What is known and what is new?

- For advanced pancreatic cancer, the first-line chemotherapy regimen recommended by international guidelines is FOLFIRINOX regimen (irinotecan + fluorouracil + calcium folinate + oxaliplatin) or AG regimen (gemcitabine + albumin bound paclitaxel).
- Our cases highlight a potential alternative treatment option in the setting of pancreatic cancer with wild KRAS and mutant BRCA.

What is the implication, and what should change now?

- This case provides new insight into first-line treatment options for advanced pancreatic cancer. Future studies with large sample size are needed to validate these discoveries.

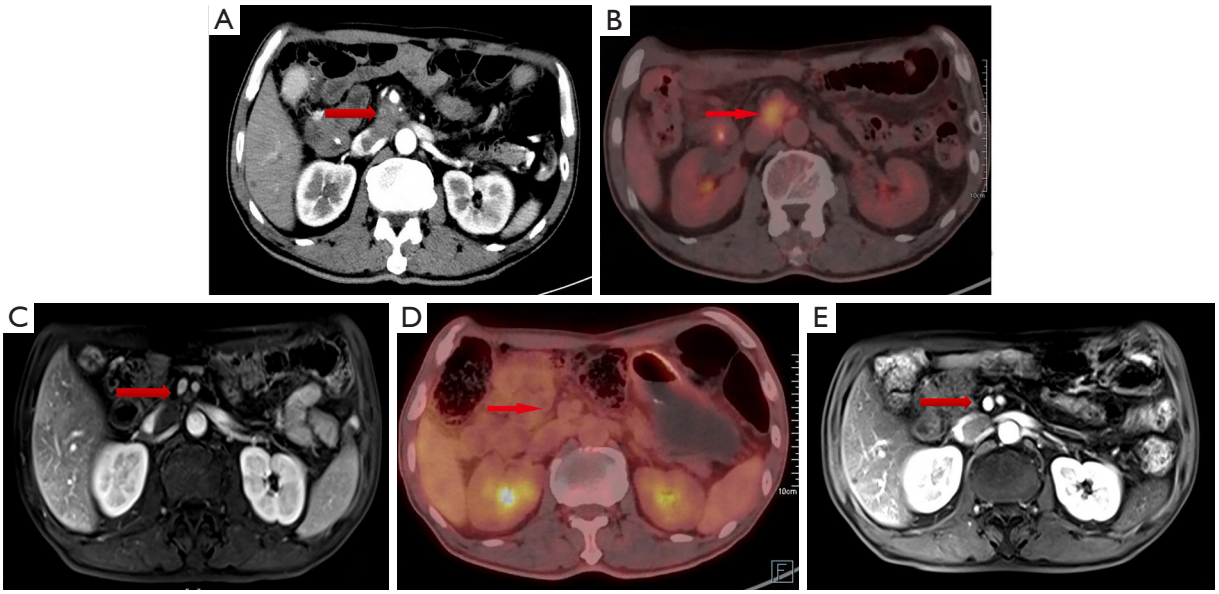

Figure 1 The comparison of upper abdominal imaging before and after chemotherapy with gemcitabine, oxaliplatin and nimotuzumab (Case 1). (A) The enhanced CT of upper abdomen showed that the lymph nodes behind superior mesenteric artery were enlarged and enhanced (red arrow). (B) The PET-CT showed that the enlarged lymph nodes with increased FDG metabolism (SUVmax =7.1) located at the same site as upper abdominal CT (red arrow). (C) After two cycles of chemotherapy, the enhanced MRI showed the metastatic lymph nodes were significantly reduced (red arrow). (D) After three cycles of chemotherapy, the metastatic nodules were not displayed by PET-CT (red arrow). (E) Enhanced MRI showed no recurrence at 13 months after chemotherapy (red arrow). CT, computed tomography; PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose; SUVmax, maximal standard uptake value; MRI, magnetic resonance imaging.

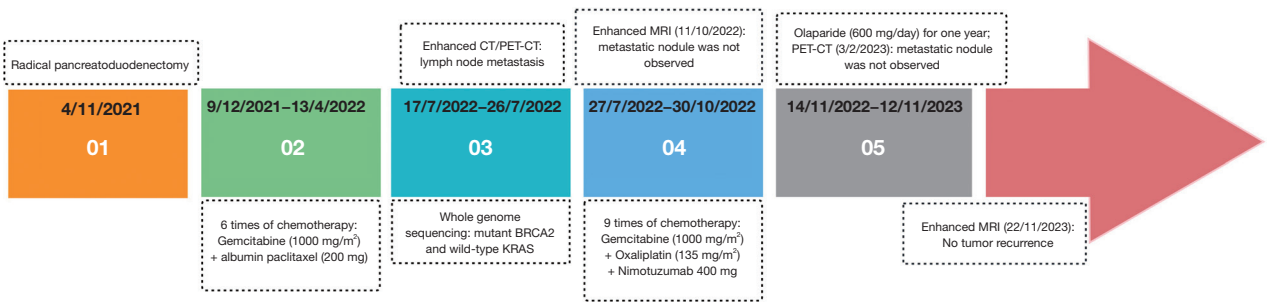

Figure 2 Timeline of major clinical events since diagnosis to present day in Case 1. CT, computed tomography; PET-CT, positron emission tomography-computed tomography; BRCA, breast cancer susceptibility gene; KRAS, Kirsten rat sarcoma viral oncogene homolog; MRI, magnetic resonance imaging.

more than 1.5 years to date without local recurrence or distant metastasis in the follow-up (*Figures 1E,2*).

Case 2, a 65-year-old man, presented with left upper abdominal pain for half a year. He suffered from hypertension, and had no other medical history. He had no family history of malignant tumors. The blood routine test, liver and kidney function tests and tumor marker tests (AFP, CEA, CA199, CA125) yielded normal results. The contrast-enhanced CT and MRI of the upper abdomen showed pancreatic body and tail cancer with multiple metastases and cysts in the liver (*Figure 3A,3B*). No metastasis was observed in thoracic CT. The metastatic

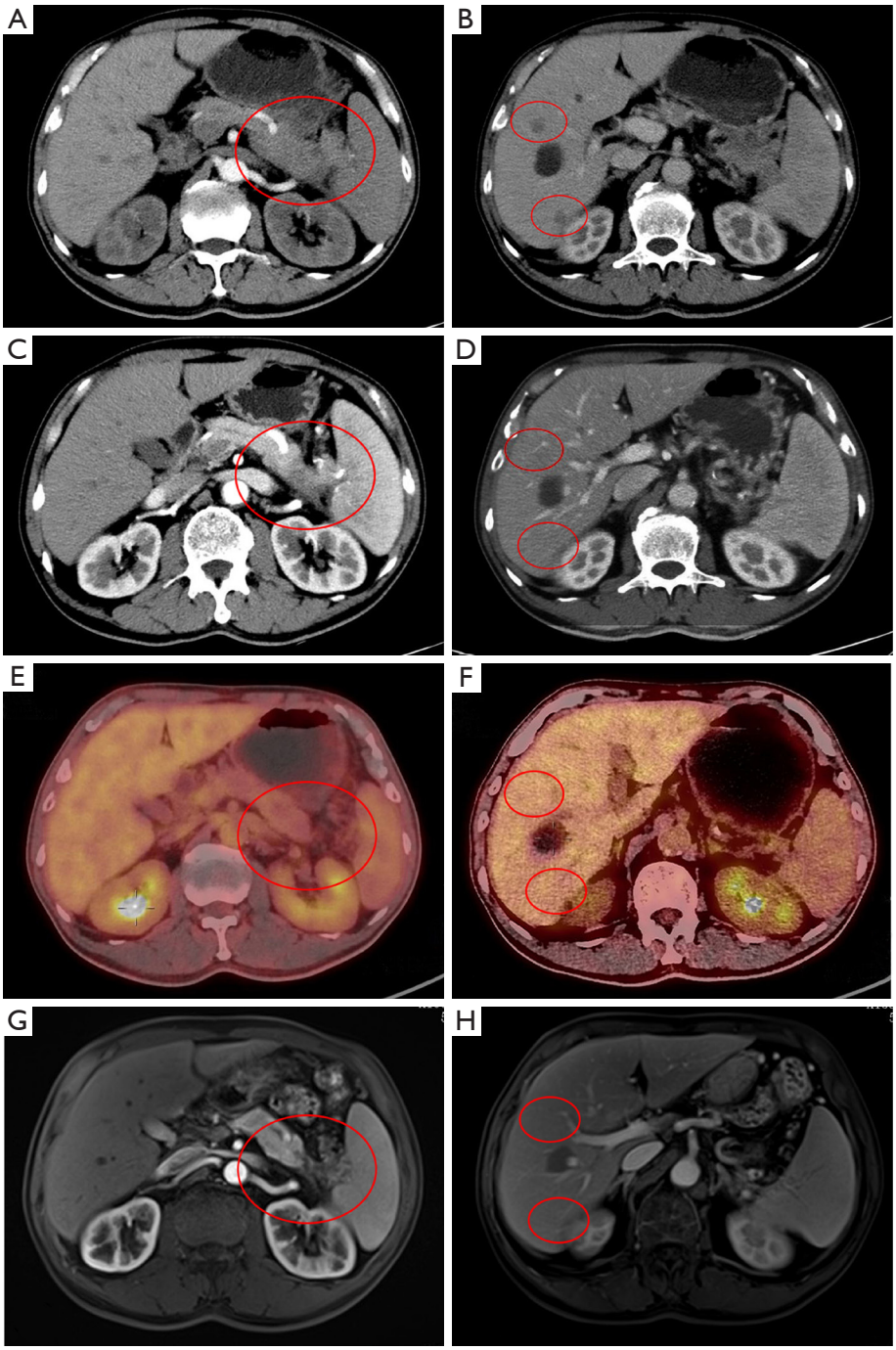

Figure 3 The comparison of upper abdominal imaging before and after chemotherapy with gemcitabine, oxaliplatin and nimotuzumab (Case 2). (A,B) The tumor at the tail of pancreas accompanied with multiple intrahepatic metastases were shown by enhanced CT of upper abdomen (red circles). (C,D) After five times of chemotherapy, the enhanced CT showed that the tumor at the tail of pancreas was significantly reduced with the liver metastatic nodules disappeared (red circles). (E,F) After nine times of chemotherapy, the PET-CT detected no obvious abnormality of FDG metabolism in the pancreas and liver (red circles), and also detected kidney stone and liver cyst (cross cursor). (G,H) Enhanced MRI showed no tumor progression at 10 months after chemotherapy (red circles). CT, computed tomography; PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging.

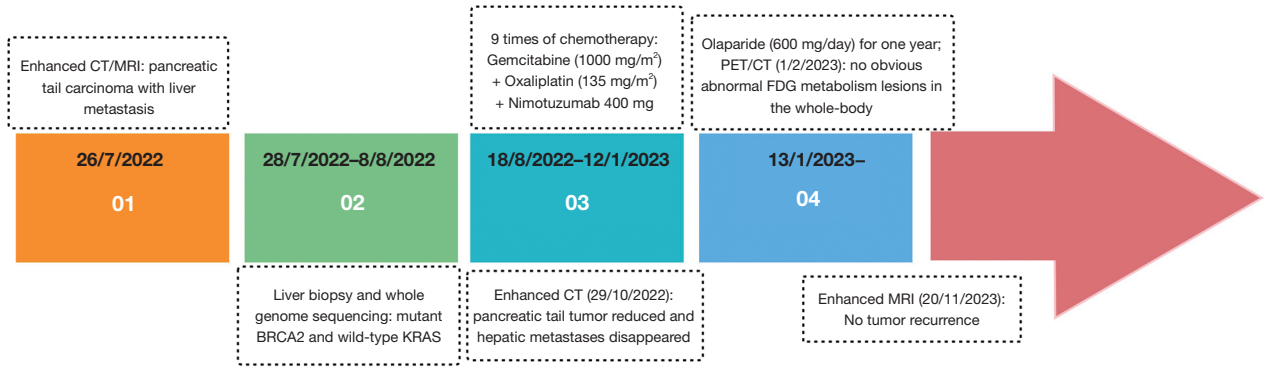

Figure 4 Timeline of major clinical events since diagnosis to present day in Case 2. CT, computed tomography; MRI, magnetic resonance imaging; BRCA, breast cancer susceptibility gene; KRAS, Kirsten rat sarcoma viral oncogene homolog; PET, positron emission tomography; FDG, fluorodeoxyglucose.

nodules in the liver were biopsied, and pathological investigation showed adenocarcinoma infiltration. He was diagnosed with advanced pancreatic adenocarcinoma (cTNM stage IV, according to 8th edition of the AJCC staging system). And the whole genome sequencing of biopsied tumor tissue revealed somatic BRCA2 mutation and wild-type KRAS gene. Immunohistochemistry showed the tumor tissue was negative for EGFR. Then, the patient received chemotherapy with gemcitabine (1,000 mg/m^2) + oxaliplatin (135 mg/m^2) + nimotuzumab 400 mg (once every 2 weeks). After five times chemotherapy, the upper abdominal enhanced CT showed that the primary tumor of pancreas was significantly reduced (*Figure 3C*), and the hepatic metastases disappeared (*Figure 3D*). After nine times of chemotherapy, PET-CT showed that there were no obvious abnormal FDG metabolism lesions in the whole-body including pancreas and liver (*Figure 3E,3F*), indicating the patient achieved complete remission (CR). During chemotherapy, the patient suffered from numbness and decreased platelets, which were significantly relieved after treatment with mecobalamin, VitB1, VitB12 and recombinant human thrombopoietin. Subsequently, the patient underwent oral administration of olaparide (600 mg/day) for one year. The patient has survived for more than 1.5 years so far with no tumor progression (*Figures 3G,3H,4*).

Ethical consideration

All procedures performed in this study 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 patients 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

Chemotherapy plays an important role in the transformation therapy, neoadjuvant therapy and adjuvant therapy of pancreatic cancer, which has prolonged the survival of patients with pancreatic cancer. With the progress of gene detection technology and its widespread application in diagnosis and treatment of tumor, the concept of individualization and precision is drawing more and more attention in the chemotherapy for pancreatic cancer, and some new targeted drugs appear. This brings new supports for optimizing clinical chemotherapeutical scheme to further prolong the survival of patients with pancreatic cancer. As reported in this study, two patients with advanced pancreatic cancer have benefited from the individual and precise chemotherapeutical scheme based on gene detection, and achieved CR and long-term survival.

The frequency of wild-type KRAS is about 10% in pancreatic cancer. The recent research results show that the pancreatic ductal adenocarcinoma with wild-type KRAS has multiple pathogenic molecules which may serve as potential therapeutic targets for targeted therapy or immunotherapy, such as EGFR and other therapeutic targets including v-raf murine sarcoma viral oncogene homologue B1 (BRAF), fibroblast growth factor receptor 1 (FGFR1), human epidermal growth factor receptor 2 (HER2) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic

subunit alpha (PIK3CA) mutations or copy number amplification (9,10). Nimotuzumab, as a monoclonal antibody targeting EGFR, can competitively bind EGFR and block its downstream signal transduction pathways. In 2017, a PCS07 clinical study from Germany compared the effect of nimotuzumab combined with gemcitabine with placebo combined with gemcitabine in the treatment of advanced pancreatic cancer, and found that gemcitabine combined with nimotuzumab significantly prolonged the median survival time (median OS: 8.6 *vs.* 6.0 months) and median PFS time (median PFS: 5.1 *vs.* 3.4 months) (7). And for pancreatic cancer patients with wild-type KRAS or high expression of EGFR, the efficacy of nimotuzumab is better (7). Qin reported a prospective, multicenter, randomized controlled clinical study aiming at exploring the clinical effect of gemcitabine combined with nimotuzumab *vs.* gemcitabine combined with placebo in the treatment of locally advanced or metastatic pancreatic cancer with wild-type KRAS (11). The results showed that gemcitabine combined with nimotuzumab could significantly prolong the median OS of patients with advanced pancreatic cancer (10.9 *vs.* 8.5 months). These studies provide the theoretical support for the use of nimotuzumab in two patients reported in our study.

The repair of DNA damage includes homologous recombination repair (HRR) and non-homologous recombination repair (NHRR). HRR uses homologous fragments to repair damaged DNA, which is a high fidelity repair process and has higher repair accuracy than NHRR. BRCAs play a vital role in HRR pathway. When BRCA genes mutate, its corresponding protein BRCA1 and BRCA2 will lose their function of HRR, leading to enhanced genomic instability and chromosome rearrangement or aberration and increased malignant transformation of normal cells (12). Compared with somatic mutations, the germline mutations of BRCA are more common in pancreatic cancer with its incidence of approximately 4–5% (13,14). Patients with mutant BRCA may benefit from platinum drugs or poly ADP ribose polymerase (PARP) inhibitors (8,15-17). While BRCA can repair double strand DNA damage of tumor cells induced by platinum drugs through the HRR pathway, tumor cells with BRCA mutation are more sensitive to platinum drugs (18). PARP can recognize and repair single strand DNA damage. In addition to the repair deficiency of double strand DNA damage in tumor cells with mutant BRCA, PARP inhibitor (PARPi) blocks the repair pathway of single strand DNA damage, resulting that tumor cells with mutant BRCA are more sensitive to PARPi than wild-type BRCA (12). In 2015, a prospective and multicenter clinical trial of PARPi olaparide in the treatment of recurrent pancreatic cancer with BRCA showed that the overall response rate and median OS were 21.7% and 9.8 months respectively, suggesting that olaparide monotherapy has a potential effect on pancreatic cancer with mutant BRCA (19). At the 2019 American Society of Clinical Oncology (ASCO) conference, a randomized controlled phase III Polo clinical trial (NCT02184195) investigated the efficacy of olaparide in maintenance treatment for advanced pancreatic cancer with mutant BRCA after gemcitabine plus platinum chemotherapy (20). The results showed that the median PFS was significantly prolonged from 3.8 to 7.4 months, the risk of disease progression was significantly reduced by 47%, and there were no serious adverse reactions. Therefore, our patients receive platinum-based chemotherapy and subsequent treatment of olaparide.

The missense mutations in TCF3 and ZBTB2 gene were also found in Case 1, and frameshift mutations of PIK3C2G gene were found in Case 2. So far, the clinical significance of these gene mutations is not well elucidated. Moreover, the EGFR high expression, considered as another predictor of nimotuzumab sensitivity, was detected in neither Case 1 nor Case 2. Generally, there are some side effects caused by gemcitabine, oxaliplatin or nimotuzumab, including nausea, vomiting, diarrhea, myelosuppression, peripheral neuropathy, etc. However, the combination of these drugs did not cause serious side effects in the presented patients. The contribution of these genetic variations and incidence of side effects should be investigated in more cases.

Conclusions

The successful treatment of two patients in this study provide a practical basis for the combined chemotherapy of gemcitabine, oxaliplatin, nimotuzumab and subsequent maintenance treatment of olaparide in the pancreatic cancer with wild-type KRAS and mutant BRCA.

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Footnote

Reporting Checklist: The authors have completed the CARE

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-24-68/coif). The 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 this study 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 patients 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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