Case Report

Durable clinical benefit from PARP inhibition in a platinum-sensitive, BRCA2-mutated pancreatic cancer patient after earlier progression on placebo treatment on the POLO trial: a case report

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Abstract: Metastatic pancreatic adenocarcinoma is a deadly malignancy with limited treatment options. Based on the results of the phase 3 POLO trial, the PARP inhibitor olaparib was approved by the Food and Drug Administration as a maintenance therapy in germline *BRCA1*- and *BRCA2*-mutated metastatic pancreatic cancer patients whose cancers had not progressed on first-line platinum-based chemotherapy. While this approval was a step forward, there have been criticisms of the POLO study leaving doubts in the field about the effectiveness of PARP inhibition in pancreatic cancer. Here, we describe a patient with a germline *BRCA2*-mutated, metastatic pancreatic cancer who was randomized to the placebo-arm of the POLO trial. After progressing on the placebo-arm of the POLO study, her cancer again responded to platinum-based chemotherapy and has since been successfully treated for 4 years with off-protocol maintenance olaparib. The presence of placebo treatment in this case serves as an internal control demonstrating the efficacy of PARP inhibition in this patient. This case highlights the potential of PARP inhibitor maintenance therapy in appropriately selected metastatic pancreatic cancer patients.

Keywords: Pancreatic cancer; PARP inhibitor; DNA repair; targeted therapy; case report

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Introduction

Metastatic pancreatic ductal adenocarcinoma (PDAC) is a nearly uniformly fatal disease with limited treatment options (1). Combinations of cytotoxic chemotherapies, such as 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine/nab-paclitaxel, have improved outcomes, but the median overall survival time for metastatic PDAC patients is still less than one year (2). Efforts to develop targeted and immunotherapeutic treatments for PDAC have been stymied by the high prevalence of *KRAS* mutations and its immunologically "cold" nature (2).

Large-scale genomic studies on germline and somatic DNA, have demonstrated that a subpopulation of PDAC patients have germline or somatic alterations in genes in the homologous recombination (HR) DNA repair pathway (3-5). Approximately 12% of pancreatic cancer patients possess a mutation within one of the "core HR genes" which cooperate in the Fanconi Anemia-BRCA pathway—*BRCA1*,

BRCA2 and *PALB2* (3,5,6). Pancreatic cancers harboring HR gene mutations are more sensitive to platinum-based chemotherapy (5,6). Importantly, patients with PDAC tumors harboring HR gene mutations, who are treated with platinum-based chemotherapy, have improved survival compared to similarly treated PDAC patients with tumors that do not harbor HR gene mutations (5,6).

Pharmacological targeting of deleterious HR gene mutations started in 2005, when two laboratories observed synthetic lethality in cancer cells with homozygous *BRCA* mutations that were treated with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors (7,8). Subsequent clinical studies demonstrated the therapeutic applicability of this result, showing that orally available PARP inhibitors were well-tolerated and exhibited potent anti-tumor activity in HR-mutated cancers (9,10). PARP inhibitors were first approved by the Food and Drug Administration (FDA) for the treatment of platinum-sensitive *BRCA*-mutated ovarian cancer. Clinical trials demonstrated that three different PARP inhibitors—olaparib, niraparib, and rucaparib—improved progression-free survival by 12–36 months compared to placebo control in the maintenance setting (11-14). PARP inhibitors have since been approved by the FDA for the treatment of HR-mutated breast and prostate cancers (15,16).

The increasing recognition that a subset of PDAC also harbors HR gene mutations inspired efforts to therapeutically exploit this molecular vulnerability (17). Early clinical trials made the important observation that, as in the case of ovarian cancer, PARP inhibitor responses in PDAC were seen almost exclusively in platinum-sensitive cancers (18-20). Building on this observation, the Phase III, randomized, placebo-controlled Pancreas Cancer Olaparib Ongoing (POLO) trial (NCT02184195) was designed to test olaparib as a maintenance therapy in germline *BRCA1*- and *BRCA2*-mutated metastatic PDAC patients whose cancers had not progressed on first-line platinum-based chemotherapy (21). Maintenance olaparib increased median progression-free survival by 3.6 months compared to placebo control, leading to FDA approval of maintenance olaparib for the treatment of germline *BRCA*-mutated metastatic pancreatic cancer in December 2019. Consistent with the results of the POLO trial, advanced pancreatic adenocarcinoma patients with germline and somatic *BRCA1*, *BRCA2*, and *PALB2* mutations treated with maintenance rucaparib had a median progression-free survival of 9.3 months in a single-arm Phase II clinical trial (22).

In this report, we describe a patient with germline *BRCA2*-mutated, metastatic PDAC who has benefited from maintenance olaparib for over 4 years. Importantly, the patient's previous progression on the placebo arm of the POLO study serves as an internal control clearly demonstrating the benefit of maintenance PARP inhibition in this case.

We present the following case in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-197).

Case presentation

A 52-year-old woman with no significant past medical history presented with right lower quadrant abdominal pain. A computed tomography (CT) scan revealed a 3.3-cm pancreatic body mass and a 2.5-cm abdominal wall nodule, along with possible peritoneal carcinomatosis. A diagnostic laparoscopy visualized multiple peritoneal nodules. Biopsies of a peritoneal metastasis and the abdominal wall nodule demonstrated adenocarcinoma consistent with a pancreatic primary. Peritoneal washings were also positive for adenocarcinoma. Her serum CA 19-9 was 1,081 U/mL.

The patient was of Eastern European descent and was not of Ashkenazi Jewish ancestry. The patient's brother died of pancreatic adenocarcinoma at the age of 42. Germline genetic testing performed on the patient showed a *BRCA2* c.2808_2811delACAA alteration. Attempts to sequence the somatic DNA from her tumor were unsuccessful.

The patient was initially treated with first-line FOLFIRINOX (*Figure 1*). Her cancer responded well to FOLFIRINOX. Radiologically, there was an 89% reduction in her tumor volume, per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, with a 67% reduction in the size of her pancreatic mass and a complete response in the abdominal wall nodule (*Figure 2*). Her serum CA 19-9 nadired at 12 U/mL. Because of neuropathy, oxaliplatin was stopped after cycle 10. The patient continued on 5-FU/leucovorin/irinotecan briefly, but all chemotherapeutic treatments were stopped after cycle 12 because the patient wanted to recover from the cumulative toxicities of chemotherapy. Following a two-month break from chemotherapy, the patient elected to enroll in the double-blind, placebo-controlled POLO trial evaluating maintenance olaparib in germline *BRCA*-mutated patients. The patient remained in the POLO trial for 5 months. At the end of the 5 months, the patient experienced progressively worsening abdominal pain and her CA 19-9 levels climbed to 174 U/mL (*Figure 1*). Restaging CT scans

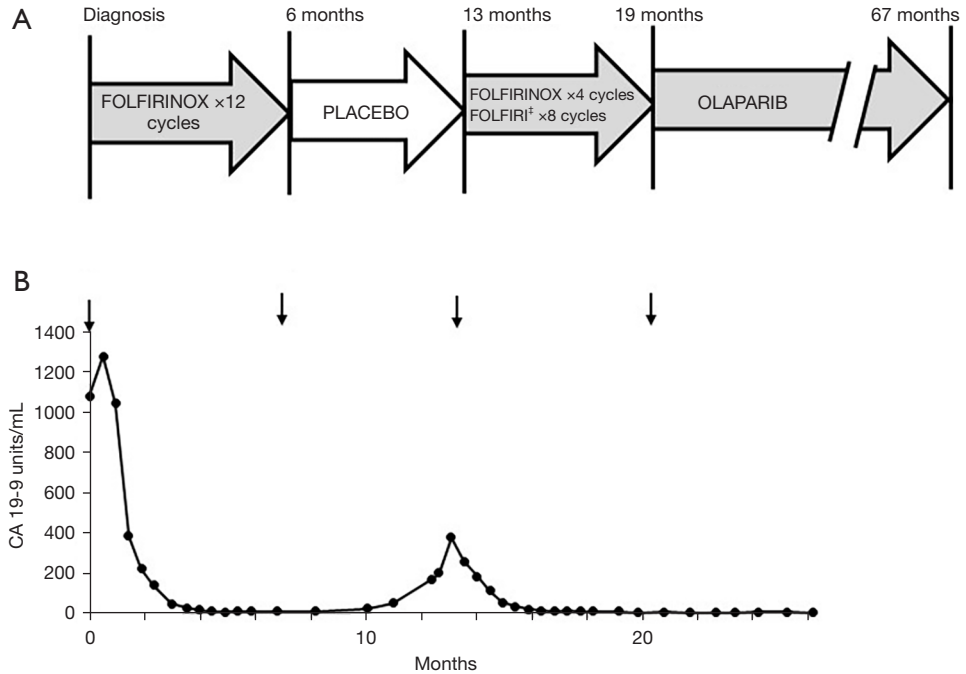

Figure 1 Treatment history and serological CA 19-9 response of a pancreatic cancer patient with a germline BRCA2 mutation. (A) Timeline depicting the treatment course and duration of therapy; (B) graphical depiction of serial CA 19-9 measurements over the course of treatment. Arrows correspond to time points when a new treatment was started in the clinical timeline presented in (A). FOLFIRI‡ indicates 5-fluorouracil/liposomal irinotecan.

showed an increase in size of the pancreatic mass, and the patient was taken off the POLO trial (*Figure 2*).

The patient was subsequently re-treated with FOLFIRINOX. After cycle 4 of FOLFIRINOX, the oxaliplatin was stopped and the patient was continued on 5-FU/leucovorin/liposomal irinotecan. The patient's tumor again responded well to chemotherapy and CT scans demonstrated a radiologic complete response to therapy (*Figure 2*). Her serum CA 19-9 level fell to 14 U/mL (*Figure 1*). While the cancer responded well to chemotherapy, the patient increasingly struggled with the cumulative toxicities of therapy and requested a chemotherapy holiday after the 8th cycle of chemotherapy.

A request was made to the sponsor of the POLO study to unblind the treatment the patient received, and it was revealed that she was in the placebo arm of the POLO study. The patient was then started on off-protocol olaparib. The patient tolerated the olaparib well with an excellent quality of life. As of this report, she has been on olaparib for 4 years. CT scans have continued to show a complete response and her CA 19-9 levels have been normal, with a range of 5–12 U/mL, throughout the course of olaparib maintenance therapy (*Figures 1*,*2*).

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.

Discussion

Metastatic PDAC has earned its reputation as a recalcitrant malignancy with limited treatment options and a dismal prognosis (1). In a step forward, the POLO trial demonstrated that olaparib maintenance therapy improved progression-free survival of patients with germline *BRCA1*- and *BRCA2*-mutated pancreatic adenocarcinoma (21). However, unlike the dramatic benefits seen in ovarian cancer patients, the median progression-free survival benefit for pancreatic cancer patients was 3.6 months (21). Furthermore, compared to placebo-treated patients, there was no improvement in overall survival in olaparib-treated PDAC patients (21,23). One possible explanation for the modest progression-free survival benefit is that germline

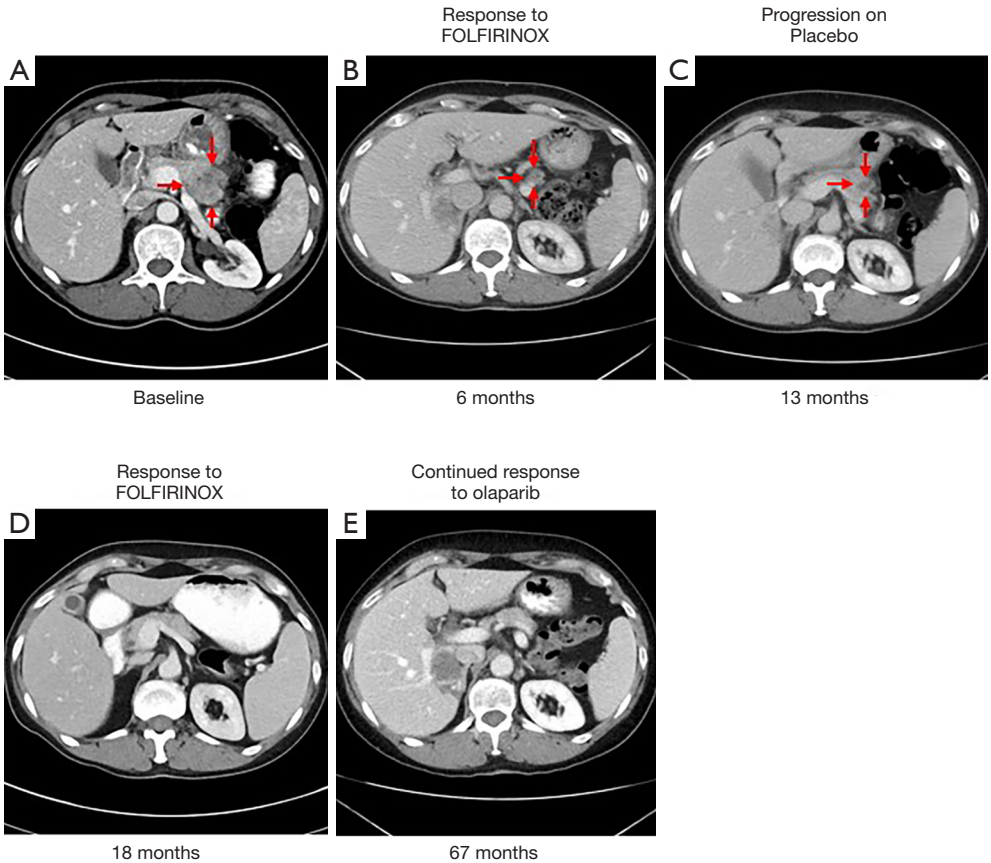

Figure 2 CT scans demonstrating the radiological response of the pancreatic tumor to therapy over the course of treatment. Arrows indicate the location of the pancreatic tumor. FOLFIRINOX, 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin; CT, computed tomography.

BRCA-mutated pancreatic cancer may continue to have sustained response following a response to platinum-based chemotherapy. Supporting this assertion is the observation that on the POLO trial the 24-month progression-free survival rate for placebo was 9.6%. However, the patient described in this report had significant progression while receiving placebo with symptomatic, radiologic and biochemical progression after 5 months. Despite the aggressive proclivity of this patient's malignancy, she was able to benefit from a renewed response to platinum-based therapy and then enjoy a remarkably durable response to olaparib for over 4 years to date. In addition to her oncologic benefit, this patient has maintained a very good quality of life while receiving olaparib after previously abandoning multi-agent chemotherapy due to accumulated toxicity. Given her excellent tolerance on olaparib, the therapeutic plan is for her to continue on olaparib indefinitely as long as it continues to control her cancer.

In the POLO trial, pancreatic cancer patients who had a radiological partial response to maintenance olaparib had an impressive median duration of response of 24.9 months, compared to the 3.7-month median duration of response for the placebo group (21). However, while olaparib clearly had activity in the 20% of pancreatic cancer patients who achieved a partial response to PARP inhibition, the olaparib-treated group as a whole had only a modest 3.6-month median progression-free survival improvement over the placebo group (21). The disparity of clinical benefit documented in the POLO trial highlights the need for better clinical indicators to select pancreatic patients for maintenance PARP inhibitor therapy. While the POLO study resembles the PARP inhibitor maintenance strategy performed in ovarian cancer trials, the efficacy in these two disease populations is different (3.6 *vs.* 12–36 months,

respectively) (11-14). An important difference between the pancreatic and ovarian cancer trials is how "platinum-sensitive" is defined (11-14). In PARP inhibitor maintenance trials for ovarian cancer, "platinum-sensitive" referred to patients who had at least a partial response to platinum-based chemotherapy (11-14). The threshold for platinum sensitivity was lower in the POLO study; patients were only required to have no evidence of radiological disease progression following at least 16 weeks of platinum-based chemotherapy to be classified as having platinum-sensitive cancer (21). However, surprisingly, on the POLO trial, patients who achieved a radiological response to first-line platinum-based chemotherapy did not have superior progression-free survival compared to patients who had stable disease on first-line platinum-based chemotherapy. Future studies are needed to better define the radiological response parameters of platinum-based chemotherapy that most accurately predict a therapeutic response to PARP inhibitors in PDAC patients. We hypothesize that a deep radiological response to platinum-based chemotherapy, such as the 89% and 100% reduction in tumor volume in this patient's two courses of FOLFIRINOX, could be a more accurate biomarker for PARP inhibitor sensitivity in the *BRCA*-mutated pancreatic cancer population.

While the POLO trial only analyzed pancreatic cancer patients with germline *BRCA1* and *BRCA/2* mutations, a recent trial of maintenance rucaparib has also demonstrated responses of pancreatic cancer patients with somatic *BRCA* and *PALB2* mutations (22). However, more research is needed to determine if tumors with germline HR gene mutations are more sensitive to PARP inhibition than tumors with somatic HR gene mutations. Germline HR gene mutations are often assumed to have greater PARP inhibitor sensitivity because there is a higher probability of biallelic inactivation, but this has not been empirically tested. Furthermore, prospective clinical data are needed to assess whether other predictive biomarkers of PARP inhibitor sensitivity, such as biallelic inactivation of HR genes, genomic HRD assays, genomic signature assays of signature 3, or functional assays of HR deficiency, are effective in selecting pancreatic cancer patients who will benefit from PARP inhibitor therapy (6,24).

Germline *BRCA2* mutations occur in up to 5% of pancreatic cancer patients and are the most common type of HR gene mutations (5,6,25). The *BRCA2* c.2808_2811delACAA mutation found in this patient is one of the most common *BRCA2* mutations in non-Ashkenazi Jews with breast cancer (26). The frameshift mutation occurs in the RAD51-binding domain of *BRCA2* on exon 11 and causes a truncated BRCA2 protein. An important function of BRCA2 is binding to DNA double-strand breaks and acting as a scaffold for the formation of RAD51 filaments, which mediate DNA repair through homologous recombination (27). Interestingly, Labidi-Galy *et al*. reported that among ovarian cancer patients with germline *BRCA2* mutations, patients with germline exon 11 *BRCA2* mutations had improved survival compared to ovarian cancer patients who were not carriers of *BRCA2* germline mutations (28). In a case series examining PARP inhibitor sensitivity in pancreatic cancer patients, Borazanci *et al*. found that 4 pancreatic cancer patients, who were carriers of germline *BRCA1* or *BRCA2* mutations involving the RAD51-binding domain, were particularly sensitive to PARP inhibitors, and had a median overall survival time of 24 months (29). Further studies are needed to establish if *BRCA2* mutations involving the RAD51-binding domain are predictive of increased sensitivity to PARP inhibition.

In conclusion, this case highlights that platinum-sensitive, germline *BRCA*-mutated patients with advanced PDAC can be exquisitely sensitive to PARP inhibition. Despite progressing on placebo in the POLO trial, the patient had a substantial radiological response to two separate courses of FOLFIRINOX and benefited from olaparib maintenance therapy for 4 years. Future studies are needed to better identify predictive biomarkers that can effectively distinguish pancreatic cancers that are sensitive to PARP inhibition.

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Footnote

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