Case Report

Excellent Response to Olaparib in a Patient with Metastatic Pancreatic Adenocarcinoma with Germline *BRCA1* Mutation after Progression on FOLFIRINOX: Case Report and Literature Review

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Keywords

Pancreatic adenocarcinoma · Germline mutations · *BRCA* · PARP-Inhibitor · Platinum sensitiveness · FOLFIRINOX

Abstract

Metastatic pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis. Until recently, cytotoxic chemotherapy was the only treatment option. Currently, there are subgroups of patients with PDAC either with somatic or germline mutations who are candidates for targeted agents. Germline mutations in the *BRCA1* and *BRCA2* genes promote the incapacity of tumor cells to recover from DNA-accumulated damage caused by cytotoxic drugs, like platinum agents, and, most recently, through a diverse process by poly(adenosine diphosphate-ribose) polymerase inhibitor (PARPi). A 59-year-old female who was treated for a triple negative breast cancer 8 years ago with surgery, adjuvant chemotherapy and radiotherapy, presented with increasing back pain. Investigation revealed multiple liver nodules and a large mass in the head of the pancreas. Biopsy confirmed PDAC. She received 13 cycles of FOLFIRINOX, achieving partial response both in the liver and pancreatic lesion, with resolution of symptoms. Due to increasing neuropathy, chemotherapy was stopped, and the patient was followed. Sixteen months later, her CA19-9 levels increased. Given limiting neuropathy, the patient was restarted on FOLFIRI only. After 8 cycles, there was disease progression plus uncontrolled back pain. A mutational test was requested and confirmed a *BRCA1* germline mutation. The patient was started on olaparib. After 3 cycles, images showed a significant response and after 6 cycles, it remained stable, with persistent fall in CA19-9 levels. She is currently on treatment, with ongoing response. In conclusion, patients with metastatic PDAC and

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BRCA mutation may benefit from PARPi even after progression on chemotherapy. We hypothesize that olaparib works even in the setting of disease progression and not solely as a maintenance therapy following platinum-based therapy. Randomized trials are needed investigating the role of olaparib following disease progression in PDAC.

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Introduction

Metastatic pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis and is responsible for 4 and 7.5% of all cancer deaths in Brazil [1] and the USA [2], respectively. According to GLOBOCAN, PDAC is the world's eighth cause of cancer deaths in both sex [3], with a 5-year survival rate of only 8% [4]. Until recently, no actionable genetic alteration was known in this disease and systemic cytotoxic chemotherapy was the only treatment option in the metastatic setting. However, emerging data from genome sequencing has identified subgroups of patients with PDAC, either with somatic or germline mutations who are potential candidates for targeted agents.

Mutations in the *KRAS* gene are the most common genetic alteration in PDAC, accounting for more than 90% of them [5]. However, no RAS inhibitor has reached clinical practice yet. In addition, DNA mismatch repair genes carry mutations in up to 2–3% of pancreatic cancers [5]. In most cases, they are related to Lynch syndrome [6], carry a slightly better prognosis compared to usual PDAC [7] and tend to respond poorly to 5-fluorouracil [8]. However, excellent responses to immunotherapy have been reported in those tumor types [9, 10].

Germline losses of function in the *BRCA1* and *BRCA2* genes are present in approximately 7% of PDAC [11]. *BRCA* genes code for proteins involved in homologous recombination repair of DNA double-strand breaks [12]. Cells that carry homologous recombination repair deficiencies can be more susceptible to damage when exposed to cytotoxic drugs – like platinum agents. Recently, the poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) revealed a diverse mechanism of action in tumor cells bearing mutations in the homologous recombination repair mechanisms. By interrupting the PARP complex enzymes, these drugs may block base excision repair mechanisms, impeding homologous recombination repair by trapping the PARP1 enzyme and leading to increasing errors in the non-homologous repair way [13, 14]. All those actions may kill *BRCA1* and *BRCA2* mutated tumor cells.

Here we present the case of a patient who had initially achieved a great response to first-line FOLFIRINOX and, after a chemo-holiday of more than 1 year, developed disease progression and was restarted on FOLFIRI with disease progression. After the knowledge of her *BRCA* mutation status, the PARPi olaparib was initiated leading to an impressive response. A consent form was obtained from the patient, granting disclosure of data and images.

Case Report

A 59-year-old female was first seen at our Institution with poor quality of life due to uncontrolled back pain. It started in 2016, when investigational computed tomography (CT) scan revealed multiple liver nodules (the largest one in segment VII measuring 3.8×2.4 cm) as well as a 5.0×4.7 cm mass in the head of the pancreas. Her personal history brought a diagnosis of breast cancer, triple negative subtype, treated with surgery, adjuvant chemotherapy and radiotherapy, 8 years before the symptoms began.

Biopsy of a liver nodule confirmed a metastatic PDAC. From November 8, 2016 to May 31, 2017 she received 13 cycles of FOLFIRINOX, achieving a very good partial response both

in the liver and pancreatic lesion, with resolution of her back pain. Due to increasing oxaliplatin-induced neuropathy, chemotherapy was stopped, and the patient was followed up with imaging and CA19-9 measurements every 3 months. In October 2018, 16 months after chemo-holiday, despite disease stability, her CA19-9 levels increased. Given limiting neuropathy, it was felt that oxaliplatin could not be reintroduced and the patient was restarted on FOLFIRI only. After 8 cycles, there was disease progression. On June 2019, magnetic resonance imaging (MRI) revealed disease progression per RECIST, as well as an increase in the tumor marker: CA19-9 1,158 U/mL.

After the first appointment in our Institution, because of the patient's previous history of breast cancer and the long period of chemotherapy break after first-line treatment, a *BRCA* mutational test was requested. It confirmed a *BRCA1* germline mutation – c.5266dupC (p.Gln756Profs*74; BIC 5382insC; rs80357606 in exon 20).

On June 11, 2019, she was started on olaparib 300 mg p.o. b.i.d. At the beginning of the second cycle, her CA19-9 levels fell to 560.4 U/mL. After 3 cycles, an MRI demonstrated a significant shrinkage on both liver and pancreatic lesions (shown in Fig. 1–2). Her CA19-9 went down to 198.5 U/mL. After 6 cycles, re-evaluation showed lesions remaining stable with a new fall in CA19-9: 141 U/mL. She is currently still on olaparib, with no side effects and ongoing response.

Discussion and Conclusion

This case illustrates how patients with metastatic PDAC with *BRCA* mutation may derive benefit from both platinum-based therapy and PARPi. This molecular alteration provided her an opportunity to survive years of metastatic disease even with a long chemotherapy-holiday interval. The knowledge that *BRCA*-mutated tumors respond well to platinum agents is not new. In a retrospective study, patients with metastatic PDAC and *BRCA* gene mutation who were treated with platinum-based agents survived longer than individuals treated with non-platinum-based chemotherapy (22 vs. 9 months) [15]. Our patient remained progression-free on FOLFIRINOX for more than 22 months, including 16 months free of chemotherapy, which is far longer than unselected patients achieve on FOLFIRINOX [16]. That was only possible due to high sensitiveness of her tumor cells to oxaliplatin. Platinum agents work by causing DNA damage and, when a tumor cell already carries mutations in the DNA damage repair machinery – like mutations in *BRCA1* or *BRCA2* genes – damage will not be effectively repaired, leading to cell death [17].

Withal, when these dysfunctional mutated cells are exposed to PARPi, such as olaparib, they will ultimately die due to incapacity of recovery from accumulated DNA damage [13, 14, 18]. These drugs have already demonstrated good responses in patients with breast and ovarian cancer who carry a *BRCA* gene mutation [19, 20].

The POLO trial [21] was the first randomized phase III trial to prospectively analyze a PARPi in metastatic pancreatic cancer patients. In this trial, 7.5% of the 3,315 screened patients had a germline *BRCA* mutation and participated in the study. Before trial entry, patients could not have had disease progression during at least 4 months of first-line platinum-based chemotherapy, which made them more likely to benefit from PARPi. After screening and enrollment, 154 *BRCA*-mutated patients were randomized in a 3:2 fashion to either maintenance therapy with olaparib ($n=92$) or placebo ($n=62$), until disease progression or death. Progression-free survival (PFS) was the primary endpoint. With data maturity of 68%, olaparib resulted in a statistically significant superior PFS of 7.4 versus 3.8 months in the placebo group, with a hazard ratio of 0.53 (95% confidence interval: 0.34–0.78) and a p value of 0.004. Olaparib use provided an overall response rate of 20 versus 12% in the placebo

Fig. 1. MRI images of target lesions: **A, C, E** Baseline. **B, D, F** Post-treatment. **A** Pancreatic lesion in enhanced axial T1 sequence. **B** Pancreatic lesion in enhanced axial T1 sequence after 3 months. **C** Pancreatic lesion in axial diffusion-weighted sequence. **D** Pancreatic lesion in axial diffusion-weighted sequence after 3 months. **E** Metastatic liver lesions in axial diffusion-weighted sequence. **F** Metastatic liver lesions in axial diffusion-weighted sequence after 3 months.

group. Two patients, both in the olaparib group, achieved a complete response (still ongoing at the time of data cutoff). In a pre-planned interim analysis, median overall survival, although still immature, was not different between the arms (18.9 vs. 18.1 months, hazard ratio of 0.91; 95% confidence interval 0.56–1.4 and p value of 0.68).

In our case, the progression-free interval after the completion of 13 cycles of FOLFIRINOX was 16 months, a period during which the patient was not receiving any anti-cancer therapy. In the placebo arm of the POLO trial, 9.6% of the patients were progression-free at 18 months, which probably reflects the magnitude of the platinum sensitiveness in this group. However, our case differs from the experimental arm of the POLO trial as olaparib was initiated when tumor was on progression. The great partial response achieved in the present case is in line

Fig. 2. Tumor marker evolution.

with data from a phase II study including 298 patients with progressive ovarian, breast, pancreatic or prostate cancer with germline *BRCA* mutations. In this trial, 23 patients with pancreatic cancer with prior gemcitabine treatment were treated with olaparib 400 mg p.o. b.i.d. Among those 23 patients, 17 had *BRCA2* mutation and the mean number of prior therapies was 2 (65% had received prior platinum). The response rate among pancreatic cancer patients was 21.7% and the stable disease rate was 34.8%. Median duration of response was 134 days [22].

The fact that the POLO trial has hyperselected its patients – they had to have a germline *BRCA* mutation and no disease progression during at least 16 weeks of the previous platinum-based treatment – makes it difficult to generalize it to all patients with metastatic pancreatic cancer. In real-life clinical practice, more than 30% of the patients are expected to have disease progression during their first 4 months of treatment with first-line FOLFIRINOX [16]. In fact, 21.7% of the patients screened for entry in the POLO trial have progressed before randomization and therefore were not included.

Subgroup analysis from POLO showed no evidence of differences with respect to the benefit of olaparib between patients who had had a response to previous platinum agents and those who had stable disease. However, it still raises the question whether patients who progress on platinum-based chemotherapy could benefit from olaparib. The only small data comes from the aforementioned non-randomized phase II trial [22], where olaparib was used after disease progression and conferred a median PFS of 4.6 months for patients with metastatic pancreatic cancer. In this study, 36.4% of the patients were progression-free at 6 months while median overall survival was 18.4 months.

In conclusion, patients with metastatic PDAC who harbor a germline *BRCA* mutation may benefit from PARPi even after progression on chemotherapy. We hypothesize that olaparib works even in the setting of pancreatic cancer disease progression and not solely as a maintenance therapy following platinum-based therapy with no disease progression. Randomized trials are needed investigating the role of olaparib following disease progression in pancreatic cancer.

Statement of Ethics

A consent form was obtained from the patient, granting disclosure of data as well as images included in this report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.R. Pimenta and D.A. Peixoto were the patient's oncologists, reviewed the literature and contributed to the manuscript drafting; S.K.N. Ueda analyzed and interpreted the imaging findings; D.A. Peixoto was responsible for the revision of the manuscript for important intellectual content; all authors issued the final approval for the version to be submitted.

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