Evidence for the Efficacy of Iniparib, a PARP-1 Inhibitor, in BRCA2-associated Pancreatic Cancer

DAVID R. FOGELMAN[1], ROBERT A. WOLFF[1], SCOTT KOPETZ[1], MILIND JAVLE[1], CHARLES BRADLEY[2], ISABEL MOK[1], FERNANDO CABANILLAS[3] and JAMES L. ABBRUZZESE[1]

[1]*Division of G.I. Medical Oncology, M.D. Anderson Cancer Center, Houston, TX, 77030, U.S.A.;*
[2]*Bipar Sciences, South San Francisco, CA 94080, U.S.A.*
[3]*Auxilio Mutuo Cancer Center, PO Box 191227, San Juan, PR 00919-1227, Puerto Rico*

Abstract. *Pancreatic cancer is an aggressive, frequently fatal malignancy that strikes 37,000 patients annually in the U.S.A. It is poorly responsive to standard chemotherapies such as gemcitabine. Approximately 5-10% of pancreatic cancer occurs in the setting of a BRCA2 mutation. Breast and ovarian carcinomas that harbor BRCA2 mutations are susceptible to the effects of an emerging class of targeted agents, namely, poly(ADP-ribose) polymerase (PARP) inhibitors. This report describes the case of a patient with a germline BRCA2 mutation and an associated pancreatic cancer treated with iniparib (BSI-201), a PARP inhibitor, who demonstrated a complete pathologic response to this agent. This case highlights the potential benefit for PARP inhibition in BRCA2-related pancreatic cancer.*

The presence of germline mutations in the *BRCA1* and *BRCA2* genes is associated with breast and ovarian cancer (1). Unlike *BRCA1*, mutations in *BRCA2* are also associated with prostate and pancreatic cancer (2, 3). Estimates of the prevalence of *BRCA2* mutations in pancreatic cancer are varied, but may be as high as 10% (4).

Patients whose tumors bear BRCA mutations may be susceptible to the effects of poly(ADP-ribose) polymerase (PARP) inhibitors, an emerging class of drugs. Recent reports have demonstrated that PARP inhibitors can effectively treat breast and ovarian carcinomas bearing BRCA mutations (5). This report describes the case of a patient with a *BRCA2*-associated pancreatic cancer treated with iniparib, a small-molecule PARP inhibitor, in combination with gemcitabine, resulting in a complete pathological response of the cancer.

Correspondence to: Assistant Professor David R. Fogelman, MD, Division of G.I. Medical Oncology, M.D. Anderson Cancer Center, 1515 Holcombe Blvd Unit 426, Houston, TX, 77030, U.S.A. Tel: +713 7922828, Fax: +713 7451163, e-mail: dfogelman@mdanderson.org

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Case Report

The patient was a 64-year-old woman with a known *BRCA2* mutation (E1308X). She had been diagnosed with left-sided breast cancer at age 26 and underwent a lumpectomy, followed by mastectomy. At age 44, she had been diagnosed with right-sided breast cancer which was treated with mastectomy and radiation. Her family history was notable for early-onset breast cancer in her mother and prostate and pancreatic cancer on the paternal side of her family.

At age 61, the patient developed obstructive jaundice. Evaluation revealed a dilated common bile duct, although no mass was seen. A stent was placed with resolution of the jaundice. The patient was then referred to the University of Texas M. D. Anderson Cancer Center where an endoscopic ultrasound revealed a 2.3-cm hypoechoic mass with irregular borders at the head of the pancreas, surrounding the distal common bile duct. No superior mesenteric artery (SMA) involvement was noted. She underwent resection of this mass *via* pylorus-preserving pancreaticoduodenectomy; all margins were negative. This proved to be a moderate to poorly-differentiated pancreatic adenocarcinoma involving peripancreatic adipose tissue, the duodenal mucosa and the ampulla of vater. Four out of thirty resected lymph nodes contained cancer. Surgical staging was pT3N1M0 and the patient was then treated with adjuvant therapy on a clinical trial in the form of radiation plus fluorouracil, cisplatin and interferon (clinical trial reference #NCT00068575, http://ClinicalTrials.gov). She completed this treatment in April 2007.

The patient remained well until late 2009. At that point, she developed intermittent left-sided back pain, radiating towards the left flank. Magnetic resonance imaging (MRI) scan performed in January 2010 (Figure 1A) revealed a soft-tissue mass measuring 3.7 cm in maximum dimension at the gastrojejunostomy site. This mass was noted to encase the SMA by over 180˚. A positron-emission tomography (PET) scan performed in February 2010 (Figure 1B) demonstrated

activity at this site, with a standardized uptake value of 14.1. A biopsy of the mass was not attempted.

Based on the clinical evaluation, the patient was enrolled onto a clinical trial of gemcitabine plus iniparib for patients with recurrent *BRCA-2*-associated pancreatic cancer (clinical trial reference #NCT00422682, at http://ClinicalTrials.gov). Treatment consisted of weekly intravenous gemcitabine at 1,000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Iniparib was given intravenously at a dose of 5.6 mg/kg on days 1, 4, 8, 11, 15 and 18. The complete blood count was monitored weekly during treatment, with planned dose reductions for thrombocytopenia and leucopenia. MRI was used to follow the treatment response.

The patient received three cycles of chemotherapy. Side-effects were mild and included mucositis, diarrhea and fatigue. One dose of chemotherapy (cycle 2, day 8) was held for neutropenia with a granulocyte count of 0.78. Imaging reassessment demonstrated that the mass had decreased in size to 1.4 cm in maximum diameter on MRI (Figure 1C) and the ^{18}FDG uptake had resolved (Figure 1D). Given the excellent response to therapy, surgery was performed with the intent of rendering the patient disease-free. Intraoperatively, only fibrotic changes at the SMA were seen; no palpable mass was identified for removal. Four lymph nodes were biopsied which contained no metastatic cancer. The patient recovered from surgery uneventfully.

The patient remained asymptomatic until July, 2010, when she developed left flank pain. A computed tomography scan in August 2010 revealed a nodal mass at the surgical bed. She has begun treatment with gemcitabine and cisplatin.

Discussion

Two aspects of this case are of particular interest. First, relative to the median disease-free survival of patients with resected pancreatic cancer and treated with postoperative chemotherapy or chemoradiotherapy, this patient had a long, 32 month disease-free survival. This is a particularly long disease-free interval for this disease and may reflect the efficacy of the DNA-damaging agents (cisplatin and radiation) used in her adjuvant regimen. Second, while the efficacy of PARP inhibition in breast and ovarian cancer has been previously demonstrated, this case is the first example (to the Authors' knowledge) of an apparently complete response of a BRCA-associated pancreatic cancer recurrence to a combination of gemcitabine and a PARP inhibitor. In the absence of continued treatment, however, the disease quickly recurred.

Loss of BRCA1 and BRCA2 protein function through germline mutations renders cells deficient in DNA repair by homologous recombination (HR) (6, 7). It is not clear why these mutations result in slightly different patterns of malignancy. What is clear is that loss of either BRCA1 or BRCA2 results in genomic instability. Cells lacking BRCA1 are highly sensitive to irradiation and display chromosomal instability (8). BRCA2-deficient cells demonstrate sensitivity to genotoxic agents such as ultraviolet light and methylmethanesulfonate (9). Such cells may also be sensitive to DNA-damaging chemotherapies such as mitomycin-C, cisplatin, chlorambucil and melphalan (10). The increase in sensitivity may be limited to agents that cause DNA cross-links or other damage repaired by HR. In support of this observation there was no increase in sensitivity to agents such as gemcitabine, fluorouracil, etoposide or taxanes.

The deficient DNA repair found in patients with BRCA mutations contributes towards carcinogenesis, but may, at the same time, render cells sensitive to PARP inhibition. In the paradigm termed 'synthetic lethality', deficiency or suppression of either of two genes may have no effect, while silencing of both may lead to cell death (11). This paradigm may apply to BRCA patients deficient in homologous recombination. In such patients, repair of DNA must occur through other pathways, such as the base excision repair pathway. PARP-1 plays a critical role in this pathway. PARP-1 catalyzes the rapid synthesis of ADP-ribose polymers from the substrate NAD and thereby regulates DNA repair and cell proliferation. In BRCA-deficient cells, inhibition of this alternate DNA repair pathway may result in the accumulation of DNA mutations within cancer cells, leading to an inability of cells to divide and promoting apoptosis.

PARP inhibitors are now being developed for clinical use. Nascent research is evaluating the role of PARP inhibitors in BRCA-deficient tumors. One early demonstration of the potential of PARP inhibition was reported a phase I trial of olaparib in a population of patients enriched for BRCA1 and *BRCA2* mutations (5). Of 60 patients enrolled, 22 had a BRCA mutation. The study found that 63% of the treated patients had responding or stable cancer among breast, ovarian, and prostate cancer patients treated with this agent. However, no pancreatic cancer patients with BRCA mutations were treated in this study. Two BRCA carriers with cancer not typically associated with BRCA mutation (vaginal adenocarcinoma and small cell lung cancer) progressed rapidly while on study.

Iniparib, a small-molecule PARP inhibitor, has also been used in BRCA-deficient tumors. One study examined iniparib in patients with triple-negative breast cancer (12), a phenotype that may be associated with decreased BRCA protein expression and deficient HR (13). In this randomized phase II study, patients received gemcitabine and carboplatin (GC) with or without iniparib. Patients treated with iniparib and GC experienced over twice the progression-free survival of the GC-alone arm (211 *vs*. 87 days, respectively), with an improvement in overall survival as well (254 *vs*. 169 days, respectively). Iniparib added little toxicity to the regimen.

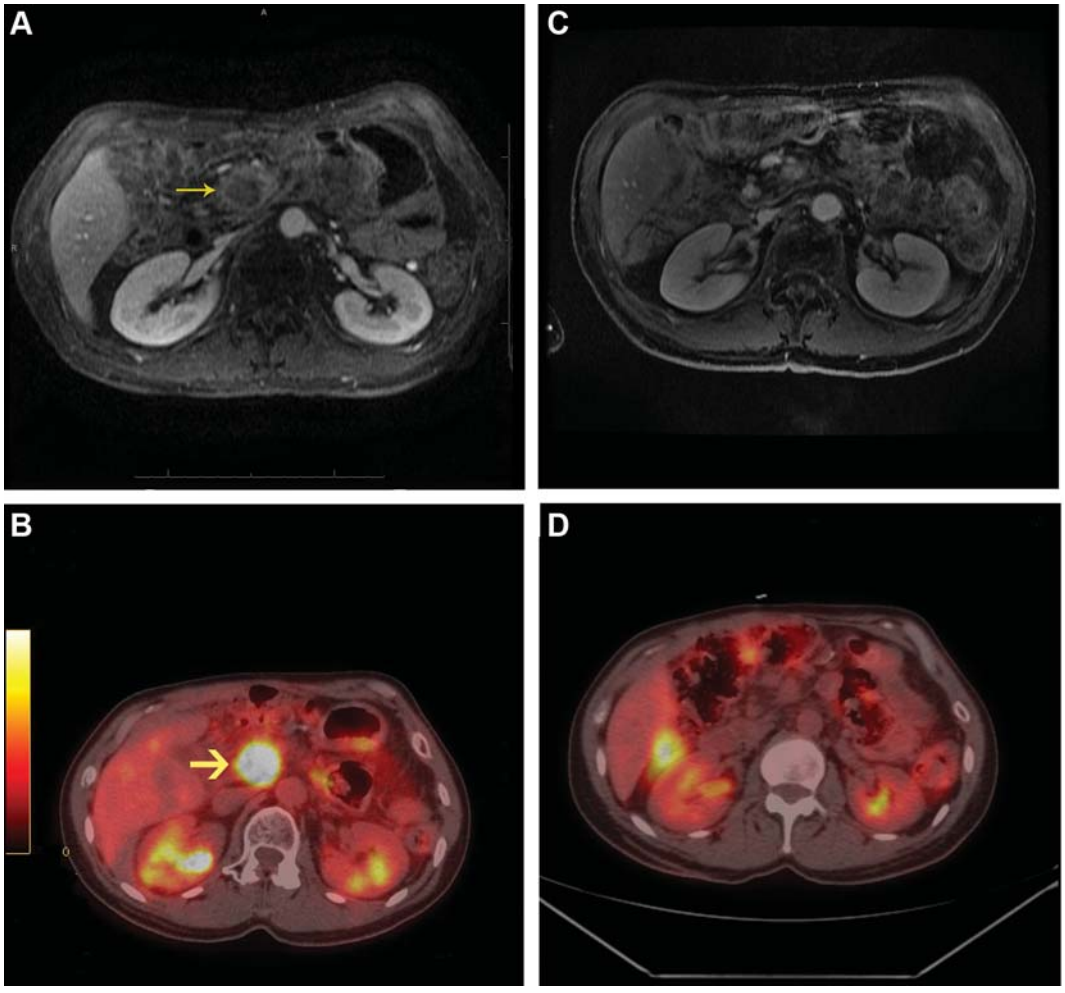

Figure 1. *A: Pre-treatment MRI demonstrating a mass at the pancreatic bed (arrow). B: Pre-treatment PET scan demonstrating a mass at the pancreatic bed (arrow). C: Post-treatment MRI demonstrating marked improvement at the pancreatic bed (circle). D: Post-treatment PET scan demonstrating resolution of PET activity (circle).*

Pancreatic adenocarcinomas are also associated with *BRCA2* mutations. Estimates of the prevalence of *BRCA2* mutations range from 6 to 10%. This number may be higher among patients with a family history of BRCA mutations; one estimate reached 15% among patients with three affected relatives (14). Ashkenazi Jews, in particular, may be at risk, as the 6174delT mutation is prevalent in this group (15). Researchers have found that 10-13% of Ashkenazi Jews with pancreatic cancer carry a *BRCA2* mutation, as compared to a 1.4% mutation rate in the general Ashkenazi Jewish population (16, 17).

There are limitations to the analysis of this patient. Although the patient did have a biopsy-proven adenocarcinoma at the time of her diagnosis, the recurrence treated with iniparib and gemcitabine was not biopsied prior to the initiation of therapy. It is theoretically possible that this was a recurrence of her breast cancer, although as this occurred near the pancreatic surgical bed, this is considered to be highly unlikely. A non-cancer-related explanation for the diagnostic studies seems also unlikely in this patient. Furthermore, the patient had not previously received gemcitabine. While responses to single-agent gemcitabine are typically not as robust as seen here, it is possible that gemcitabine was responsible for much of this improvement.

In conclusion, this patient's major radiological response to gemcitabine and iniparib suggests that *BRCA2*-associated pancreatic cancer, similar to breast and ovarian BRCA cancer, may be susceptible to PARP inhibition. Well-designed clinical trials will be needed to understand the role of PARP inhibitors with and without other cytotoxic agents in pancreatic cancer, but with these agents soon to go through the U.S.A. Food and Drug Administration approval process, clinicians caring for pancreatic cancer patients should be aware of the relationship of *BRCA2* mutations and

pancreatic cancer and be attuned to genetic testing for patients with an appropriate family history. Going forward, it will be important to identify biomarkers that may reflect broader defects in HR and, in turn, potential sensitivity to PARP inhibitors. If such biomarkers can be developed, it is possible that larger groups of patients may benefit from the incorporation of PARP inhibitors into their cancer care.

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