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Case Report
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Carboplatin & Olaparib Salvage Therapy in *BRCA*(+) Pancreatic Adenocarcinoma with Medullary & Leptomeningeal Metastasis

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Abstract

The following report depicts the case of a patient with a favorable response to carboplatin chemotherapy followed by olaparib salvage therapy for metastatic pancreatic cancer with a Breast Cancer Susceptibility Gene 2 (*BRCA2*) gene mutation. Olaparib is an orally delivered poly (ADP-ribose) Polymerase (PARP) enzyme inhibitor with Food and Drug Administration (FDA) approval in several malignancies associated with *BRCA*-mutations or Homologous Recombination Deficiency (HRD). Use of olaparib as a salvage therapy may be warranted in cases with poor response to previous chemotherapeutic regimens and can lead to extended survival benefit, substantiating the use of PARP inhibitors for patients with *BRCA* mutations and limited alternative treatment options. To our knowledge, this case represents the first example of *BRCA*-mutated pancreatic cancer with Central Nervous System (CNS) involvement responding to an olaparib-containing regimen. While various case reports and a randomized double-blinded trial have shown improvement in Progression Free Survival (PFS), further objective data regarding the benefits and associated risks of this new regimen are necessary to bolster clinical decision-making.

Keywords/Abbreviations: AJCC: American Joint Committee on Cancer; BRCA2: Breast Cancer Susceptibility Gene 2; CA 19-9: Cancer Antigen 19-9; CT: Computed Tomography; CNS: Central Nervous System; ECRP: Endoscopic Retrograde Cholangiopancreatography; EUS; Endoscopic Ultrasound; FNA: Fine Needle Aspiration; FOLFOX: [Folinic Acid, Fluorouracil, Oxaliplatin]; FDA: Food and Drug Administration; HRD: Homologous Recombination Deficiency; KRAS: Kirsten Rat Sarcoma; LM: Leptomeningeal Metastasis; MM: Medullary Metastasis; NGS: Next Generation Sequencing; PDAC: Pancreatic Ductal Adenocarcinoma; PARP: Poly(ADP-Ribose) Polymerase inhibitors; PFS: Progression Free Survival; ST: Salvage Therapy; SCC: Signet Cell Carcinoma; SBRT: Stereotactic Body Radiation Therapy; WBRT: Whole Brain Radiation Therapy

Introduction

The mortality rate from pancreatic ductal adenocarcinoma has doubled over the last 30 years with pancreatic cancer now representing the seventh leading cause of cancer death worldwide [1-3]. With approximately 80% of patients having metastatic disease at time of diagnosis and a 5-year survival rate of only 8% to 9%, treatment modalities shown to reduce mortality are ever-more important [2,4,5]. The following report depicts the case of a patient with a favorable response to carboplatin chemotherapy followed by olaparib salvage therapy for metastatic pancreatic cancer with a Breast Cancer Susceptibility Gene 2 (*BRCA2*) mutation [1,3,6]. Olaparib is an orally delivered poly (ADP-ribose) Polymerase (PARP) enzyme inhibitor with Food and Drug Administration (FDA) approval in several malignancies associated with *BRCA*-mutations or Homologous Recombination Deficiency (HRD). While various case reports and a randomized double-blinded trial have shown improvement in Progression Free Survival (PFS), further objective data regarding the benefits and associated risks of this new regimen are necessary to bolster clinical decision-making [7,8]. Use of olaparib as a salvage therapy may be warranted in cases with poor response to previous chemotherapeutic regimens and can lead to extended survival benefit.

Case Presentation

In late 2018, a 64 year-old man presented to the hospital with two weeks of fever, nausea, and

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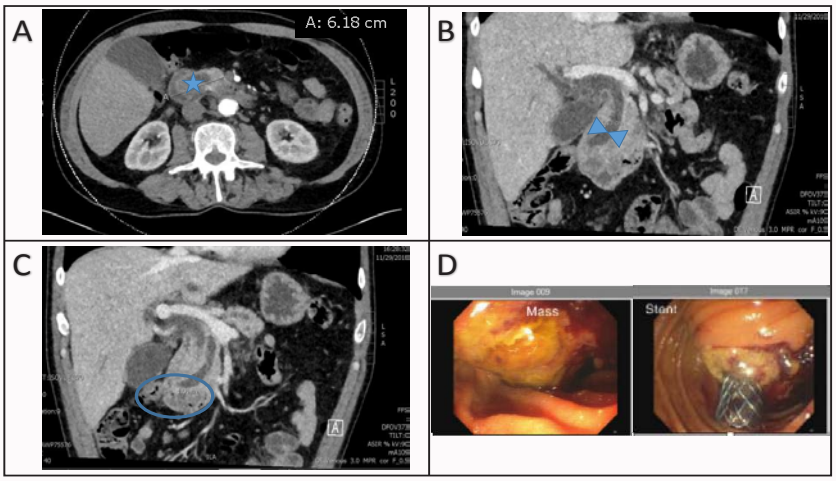

Figure 1: CT Initial diagnostic imaging and tumor visualization on endoscopic ultrasound – pancreatic head mass causing common bile duct/pancreatic duct dilation. A) CT Transverse plane showing widest tumor dimension along the pancreatic head (blue star). B) CT Coronal view showing pancreatic head mass extending into duodenum (blue circle). C) CT Coronal view showing common bile duct dilatation to 1.13 cm (blue arrowheads). D) Gross anatomic view from EUS showing pancreatic head mass protruding into duodenum before and after biliary stenting.

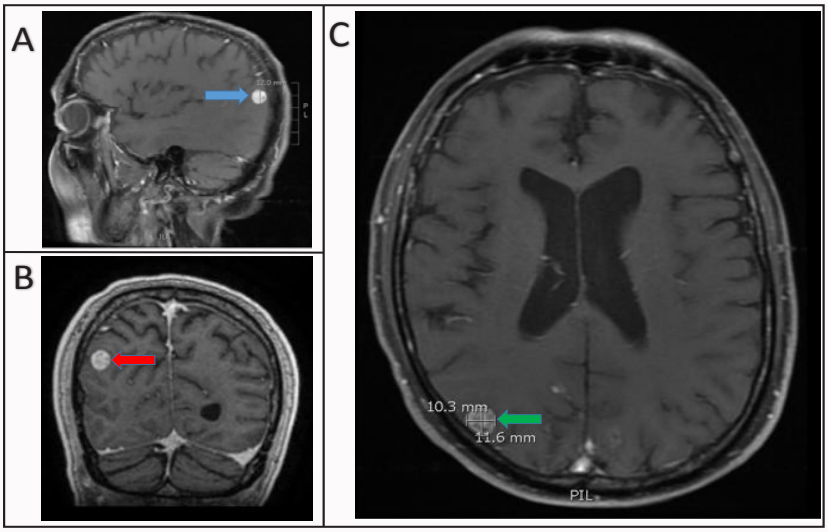

Figure 2: Leptomeningeal metastasis on MRI brain. A) Sagittal view (blue arrow). B) Coronal view (red arrow). C) Transverse view (green arrow).

painless jaundice leading to admission for suspected cholangitis. Lab work revealed pancytopenia, as well as elevated glucose, lipase, liver function enzymes, Cancer Antigen 19-9 (CA 19-9), and direct bilirubin. Computed Tomography (CT) of the abdomen and pelvis revealed a 2.5 cm × 6.2 cm × 2.0 cm pancreatic head mass causing common bile duct and pancreatic duct dilation, as well as a single focus in the right inferior lobe of the liver concerning for metastasis (Figure 1). Follow-up Endoscopic Ultrasound (EUS) and Endoscopic Retrograde Cholangiopancreatography (ECRP) revealed a dilated bile duct measuring 12 mm in diameter, multiple enlarged peripancreatic lymph nodes, and tumor extension into the duodenum found favorable for biopsy over Fine Needle Aspiration (FNA). Given the degree of anatomic distortion a biliary metal stent was placed into the bile duct exiting to the duodenum (Figure 1).

Pathology of the endoscopically-excised friable exophytic duodenal mass distal to the ampulla revealed mucinous adenocarcinoma with signet ring cell morphology. Magnetic Resonance Imaging (MRI) of the thoracic and lumbar spine revealed diffuse abnormal marrow signal concerning for bone marrow infiltration by metastatic disease. With small bowel, liver, and bone marrow involvement, the clinical presentation was consistent with a diagnosis of metastatic pancreatic adenocarcinoma.

Initial Next Generation Sequencing (NGS) revealed Kirsten Rat Sarcoma (KRAS) gene mutation (c.436G>A p.A146T) but was negative for any targetable mutations. He was initially treated with conventional regimens to include gemcitabine and nab-paclitaxel followed by Fluorouracil (5-FU) plus liposomal irinotecan on disease progression. At the 1-year mark, further disease progression led to palliative Stereotactic Body Radiation Therapy (SBRT) of liver metastases and transition to third line chemotherapy with folinic acid (leucovorin), 5-FU, and oxaliplatin (FOLFOX). Three months into FOLFOX treatment, the patient developed painful paresthesia in the distal extremities attributed to oxaliplatin-induced peripheral neuropathy. However, increasing asthenia and unsteady gait

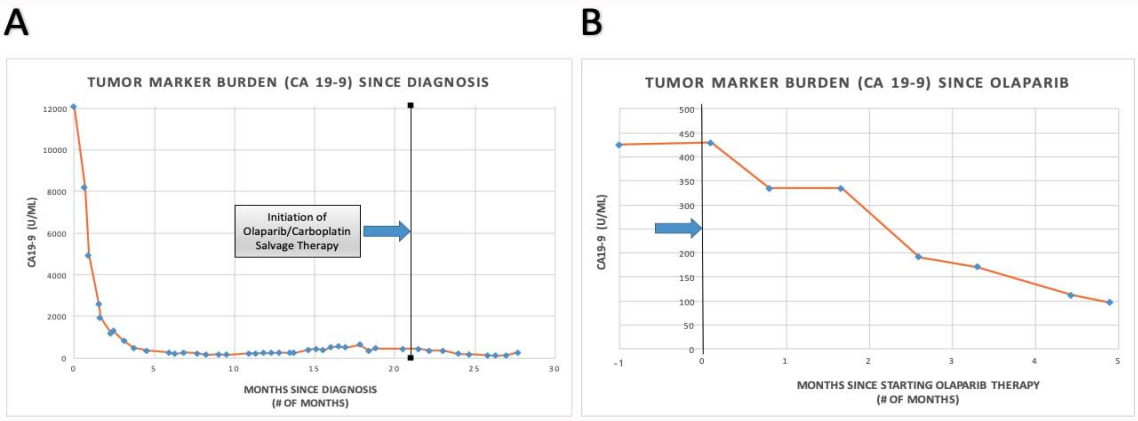

Figure 3: Trend of Tumor Marker Burden (CA 19-9). A) Since initial diagnosis. B) Since initiation of olaparib/carboplatin salvage therapy.

concerning for Central Nervous System (CNS) disease involvement led to additional diagnostic evaluation. Brain MRI revealed a right parieto-occipital cortex enhancing mass and sulci involvement suspicious for parenchymal metastasis and leptomeningeal carcinomatosis, respectively (Figure 2). He then underwent treatment with Whole Brain Radiation Therapy (WBRT).

Germline genetic testing revealed a heterozygous *BRCA2* deletion presenting the opportunity to utilize a PARP inhibitor strategy. Salvage systemic therapy with carboplatin and olaparib was pursued with a plan to transition to olaparib maintenance therapy in the event of an efficacious response. The patient is currently stable after five cycles of salvage therapy with decreasing CA19-9 antigen levels (Figure 3) and improved intra-abdominal tumor burden on repeat PET imaging. The regimen remains mostly well tolerated with resolution of prior chemotherapy-related toxicity, including peripheral neuropathy, with only mild non-limiting pancytopenia secondary to carboplatin and olaparib persisting.

Discussion

This case illustrates the utility of olaparib as salvage therapy for advanced pancreatic adenocarcinoma, particularly when combined with platinum-containing chemotherapy, such as carboplatin. Currently, FDA approval for olaparib in pancreatic cancer is limited to maintenance therapy for disease that has not progressed for at least 16 weeks on a platinum-based first-line chemotherapy regimen in the setting of a deleterious *BRCA*-mutation [7]. In this case, the development of disease progression refractory to standard therapies as well as CNS metastases warranted the pursuit of off-label PARP inhibition. Similar case reports have validated treatment response after progression on chemotherapy, substantiating the use of PARP inhibitors for patients with *BRCA* mutations and limited alternative treatment options [9]. To our knowledge, this case represents the first example of *BRCA*-mutated pancreatic cancer with CNS involvement responding to an olaparib-containing regimen.

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