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CASE REPORT

Response to a Third-Line Mitomycin C (MMC)-Based Chemotherapy in a Patient with Metastatic Pancreatic Adenocarcinoma Carrying Germline BRCA2 Mutation

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ABSTRACT

Context Gemcitabine remains the mainstay of palliative chemotherapy for those patients with unresectable or metastatic pancreatic cancer. Objective radiological responses to gemcitabine are rare and reported median survival is only about six months. New therapeutic concepts and strategies are needed in order to improve those dismal statistics.

Case report We report here a case of a patient with metastatic pancreatic cancer responding to a third-line therapy with combination of mitomycin C and capecitabine. Interestingly, the patient had a strong family history of breast cancer and tested positive to germline BRCA2 mutation.

Conclusion We feel that this is of interest because of preclinical reports of increased sensitivity of pancreatic cells carrying BRCA2 mutations to DNA-intercalating agents such as mitomycin C. Further research and clinical trials are warranted to support this novel concept.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer related deaths in the United States of America [1, 2]. Gemcitabine monotherapy has been shown to improve clinical benefit response and survival in patients with advanced pancreatic cancer. Survival rate at twelve months was 18% for patients treated with gemcitabine compared to 2% for those treated with 5-flourouracil [3]. Gemcitabine still remains one of the standard treatments for advanced pancreatic cancer. More recently, addition of erlotinib (an oral EGFR inhibitor) to gemcitabine has shown a small but statistically significant improvement in median survival [4]. For those patients who do not respond or fail gemcitabine-based therapy off protocol considerations may include fluoropyrimidines such as 5-fluorouracil or capecitabine. It is not clear if any of these approaches bring on meaningful improvement in survival or quality of life.

Breast cancer 2, early onset (BRCA2), isolated through positional cloning using data from families with inherited breast cancer, was the second breast cancer susceptibility gene to be discovered. BRCA2 is a tumor suppressor gene that is inherited in an autosomal dominant fashion with incomplete penetrance [5]. The BRCA2 gene contains 26 exons encoding a 3,418 amino acid phosphoprotein. The gene is ubiquitously expressed in a cell cycle dependent manner, with the greatest expression during the S and G2 phases of the cell cycle [6, 7]. BRCA2 can partially repress p53 dependent transcription, suggesting that it may function as a co-repressor of transcription [8]. BRCA2 is predominantly involved in DNA damage repair and is thought to interact with DSS1 and BRCA2 and CDKN1A interacting protein

(BCCIP)-alpha, both of which have been implicated in regulation of the cell cycle and cell growth [9, 10].

Mitomycin C (MMC) is an anti tumor antibiotic which forms intra-strand and inter-strand cross links in the DNA. The covalent link between the two strands prevents unwinding of DNA interferes with fundamental cellular processes of replication and transcription. The therapeutic value depends on the ability of cells to remove the crosslinks [11]. BRCA2 mutation makes the cells more susceptible to MMC by diminishing its capacity to repair the crosslinks and therefore making cancer cells more susceptible to treatment with MMC. Here, we describe a case of a clinical and biochemical (CA 19-9) response to MMC in a patient with pancreatic cancer and BRCA2 mutation, after failing multiple other therapeutics.

CASE REPORT

This is a case of a 49-year-old woman who presented with abdominal bloating and distension lasting for several months. Her prior medical/surgical history only included a cesarean section and laparoscopic hysterectomy for endometriosis. Her family history was significant for multiple cases of breast cancer involving first-degree relatives in three successive generations. Due to significant family history of breast cancer the patient was tested and found positive for one of clinically relevant BRCA2 gene mutations. A computerized tomography (CT) scan of the abdomen revealed a 3.2x1.4 cm mass in the body of pancreas, encasing the splenic artery. In addition, there were multiple hypodense lesions in the liver, consistent with metastases. A CT scan-guided biopsy of the pancreatic mass was performed and the cytopathology was consistent with a diagnosis of moderately differentiated pancreatic ductal adenocarcinoma. Biochemical laboratory analyses including glucose levels, alkaline phosphatase, bilirubin and transaminases were all within normal limits. The serum CA 19-9 was elevated at 856 U/L (reference range: 0-35 U/L). She was initially started on a clinical trial with gemcitabine in combination with another experimental cytotoxic agent (alkylator) and achieved a response. A repeat CT scan of the abdomen after completing seven cycles of therapy showed no evidence of the pancreatic mass, significant decrease in the size of liver metastases and a serum CA 19-9 level of 15 U/L. However, due to persistent neutropenia and thrombocytopenia the experimental agent had to be discontinued and she continued with gemcitabine monotherapy only. After 2 months on gemcitabine her CA 19-9 level started to rise again, pancreatic mass became visible and there were multiple new liver lesions on a CT scan. Gemcitabine therapy was discontinued and she was then enrolled in a clinical trial using an experimental anti-angiogenesis agent. Despite of this, there was evidence of further disease progression on a follow-up CT scan, she had worsening of her abdominal/back pain and her serum CA 19-9 level continued to rise. Subsequently, the patient was started on combination therapy with MMC (7 mg/m^2, i.v. every 6 weeks) plus capecitabine (825 mg/m^2, orally twice a day, for 14 days repeated every 21 day). After 14 weeks on this therapy her CA 19.9 decreased from 936 U/L to 24 U/L (Figure 1). In addition, her pain has significantly improved and her follow-up CT scan showed decrease in size of pancreatic mass and liver metastases (Figure 2). She continued on therapy for 6 months, but eventually developed persistent grade 3 thrombocyto-penia and MMC was discontinued. We felt

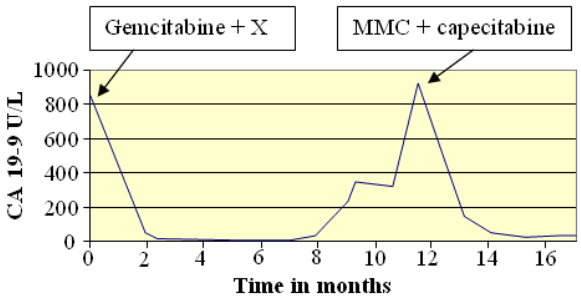

Figure 1. CA 19-9 trend over time. Initial decrease is noted following treatment with gemcitabine and an experimental drug (X). A second rapid decline in CA 19-9 level is noted after the patient was started on mitomycin C (MMC) plus capecitabine.

that this rarely seen response to third-line therapy in this patient with metastatic pancreatic adenocarcinoma could be attributed to her increased sensitivity to intercalating agents due to germ-line BRCA2 mutation.

DISCUSSION

BRCA2 mutations have been known to be associated with higher incidence of breast, ovarian and pancreatic adenocarcinoma. Initial evidence of an association between pancreatic and hereditary breast and ovarian cancer came form the observation that exocrine pancreatic cancer clustered with the breast and ovarian cancer in families [12]. This was confirmed shortly after the identification of the BRCA2 gene by finding that breast and ovarian cancer families carrying BRCA2 mutation contained an excess of pancreatic cancers relative to breast and ovarian cancer families without BRCA2 mutations [13, 14]. Although present in only a minority of pancreatic cancers, mutations in the BRCA2 gene could provide a rational target for treatment with chemotherapeutic agents.

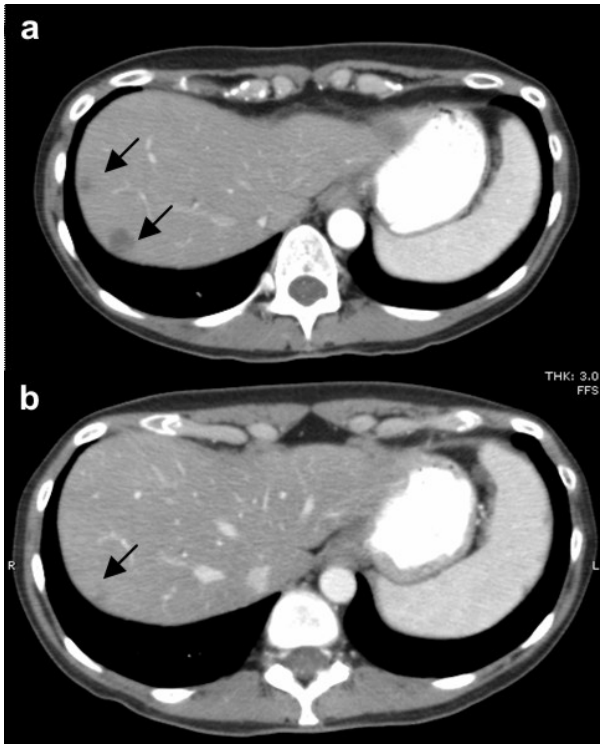

Figure 2. Two CT images before and after initiation of therapy with mitomycin C. **a.** the CT image prior to initiation of therapy showing two liver metastases (arrows). **b.** Decrease in the size of liver metastases (arrows) after 14 weeks of treatment with mitomycin C plus capecitabine.

Van der Heijden *et al*. have demonstrated that pancreatic cancer cells having defects in Fanconi anemia/BRCA2 pathway are remarkably sensitive to MMC both in culture and mice [15, 16]. Isacoff *et al*. reported good results with MMC plus fluorouracil regimen in first-line therapy of locally advanced pancreatic cancer, with two out of 50 patients achieving complete remission [17]. Another study using the same regimen in patients with metastatic pancreatic carcinoma also showed some activity including one complete remission [18]. We felt that it was important to describe this case of a meaningful clinical response to third line MMC-based therapy in a patient with who carried BRCA2 mutation. While we cannot exclude the possibility that some of the clinical benefit seen is this patient could be attributed to capecitabine, based on the existing preclinical data linking BRCA2 mutations and sensitivity to intercalators, we hypothesize that the response was likely due to MMC. Although the BRCA2 mutation is relatively rare in patients with pancreatic cancer (less than 10%) this may be an attractive therapeutic option for selected patients. Currently there is an ongoing phase II clinical trail prospectively evaluating the effectiveness of MMC therapy in pancreatic cancer patients carrying BRCA2 mutation (clinical trial identifier: NCT00386399, Sydney Kimmel Cancer Center).

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Keywords Drug Therapy; Genes, BRCA2; Mitomycin; Pancreatic Neoplasms

Abbreviations BRCA2: breast cancer 2, early onset; MMC: mitomycin C

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