# Prolonged survival in a patient with BRCA2 associated metastatic pancreatic cancer after exposure to camptothecin: a case report and review of literature

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**Germline mutations in the tumor suppressor genes BRCA1 and BRCA2 have been proven to predict a drastically increased lifetime risk of breast and ovarian cancers in the individuals who carry them. A number of studies have shown that the third most common cancer associated with these mutations is pancreatic cancer. There is evidence of in vivo therapeutic response to the cross-linking agents; such as mitomycin C (MMC) in BRCA2 mutated pancreatic cell lines. We present the 'first patient' who achieved a prolonged survival on irinotecan, a topoisomerase I poison, administered alone and then in combination with cetuximab. Our patient presented at the age of 71 years with a dual diagnosis of prostate carcinoma and pancreatic carcinoma on the background of a significant family history of cancer. On genetic testing, he was found to have the common Ashkenazi Jewish BRCA2 mutation, 6174delT. To date, he has received 22 cycles of docetaxel, capecitabine, and gemcitibine followed by single agent irinotecan every 3 weeks for 27 cycles, and then weekly cetuximab was added to the regimen at cycle 28. His disease then remained stable for an additional 13 months. He did not have mutated KRAS. MMC and oxaliplatin was then introduced upon progression. His current treatment is MMC plus irinotecan as oxaliplatin was removed because of a hypersensitivity reaction. This patient is stable with an Eastern Cooperative Oncology Group performance status of 0, four and a half years (56 months) after his initial diagnosis. DNA topoisomerases are nuclear enzymes responsible for the regulation of DNA topology. They are involved in basic DNA transactions during replication, transcription, and recombination. BRCA2-deficient human cells are deficient in the repair of double-strand breaks and DNA cross-links through homologous recombination. Active poisons of topoisomerase I include derivatives of camptothecin. Our case is the first clinical piece of evidence that demonstrates an increased sensitivity to camptothecin-11 and a reduced topoisomerase I relaxation activity in BRCA2 associated pancreatic cancer. This case shows that patients with metastatic pancreatic carcinoma and BRCA2 mutations may have disease that is biologically more chemosensitive and consequently prolong survival despite prognostically unfavorable disease. *Anti-Cancer Drugs* 20:634–638 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

BRCA2 mutations have been known to be associated with a higher incidence of breast, ovarian, and pancreatic adenocarcinoma. Initial evidence of an association between pancreatic and hereditary breast and ovarian cancer came from the observation that exocrine pancreatic cancer clustered with breast and ovarian cancer in families [1]. 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 [2,3]. Although present in only a minority of pancreatic cancers, mutations in the BRCA2 gene could provide a rational target for treatment with chemotherapeutic agents. BRCA2 is a tumor suppressor gene that is directly implicated in familial breast cancer. Extensive genetic and biochemical characterization has shown that BRCA2 is involved in the maintenance of chromosomal stability and that it has an important role in recombination-mediated double-strand DNA break repair.

Van der Heijden *et al.* [4,5] have demonstrated that pancreatic cancer cells having defects in Fanconi anemia/BRCA2 pathway are remarkably sensitive to mitomycin C (MMC) both in culture and mice. Rahden-Staroñ *et al.* [6] demonstrated an increased sensitivity of V-C8 cells to camptothecin (CPT) and a reduced topoisomerase I relaxation activity, measured in nuclear extracts from these cells. The survival of V-C8 cells in the presence of CPT, the sensitivity of V-C8 topoisomerase I to CPT and the level of the relaxation activity in V-C8 nuclear extract

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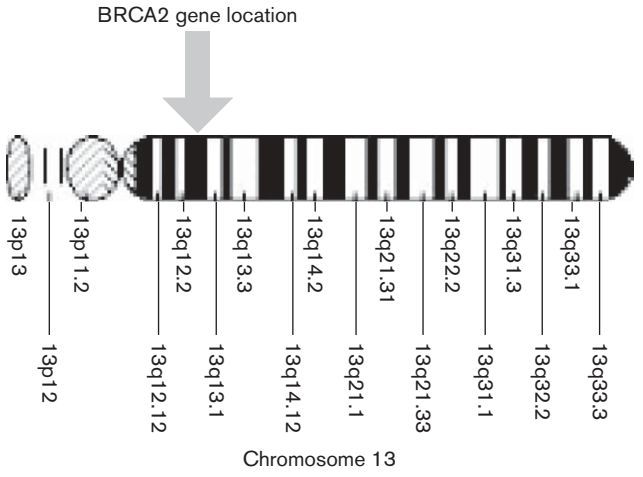
were almost completely restored by introduction of either human or murine BRCA2 gene [6].

Gemcitabine monotherapy has been shown to improve clinical response and survival in patients with advanced pancreatic cancer. Survival rate at 12 months was 18% for patients treated with gemcitabine compared with 2% for those treated with 5-fluorouracil (5-FU) [7]. Gemcitabine still remains one of the standard treatments for advanced pancreatic cancer. More recently, addition of erlotinib (an oral epidermal growth factor receptor inhibitor) to gemcitabine has shown a small but statistically significant improvement in median survival [8]. For those patients who do not respond or fail gemcitabine-based therapy, off protocol considerations may include fluoropyrimidines such as 5-FU, capecitabine, or irinotecan (CPT-11) [9]. It is not clear whether any of these approaches bring on meaningful improvements in survival or quality of life.

The BRCA2 gene, 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 [10]. The BRCA2 gene contains 26 exons encoding a 3418 amino acid phosphoprotein. The BRCA2 gene is located on the long (q) arm of chromosome 13 at position 12.3. More precisely, the BRCA2 gene is located from base pair 31 787 616 to base pair 31 871 804 on chromosome 13 (Fig. 1). 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 [11,12]. BRCA2 can partially repress p53 dependent transcription, suggesting that it may function as a corepressor of transcription [13]. BRCA2 is predominantly involved in DNA damage repair and is thought to interact with DSS1 and BRCA2 and CDKN1A interacting protein (BCCIP)-α, both of which have been implicated in regulation of the cell cycle and cell growth [14,15]. Here, we describe the 'first patient' who achieved a prolonged survival on CPT-11 administered alone and then in combination with cetuximab.

**Fig. 1**




Location of BRCA2 gene.

## Case report

A 71-year-old Caucasian male of Ashkenazi Jewish ancestry presented with a combined diagnosis of metastatic pancreatic cancer and prostate cancer. He had originally been diagnosed with prostate cancer by his primary care physician on the basis of an elevated prostate-specific antigen (PSA) on routine screening. He underwent radical prostatectomy for a diagnosis of poorly differentiated prostatic adenocarcinoma (Gleason grade 7). Postoperatively, the patient had recurrent fevers and had a contrast enhanced computed tomography (CT) scan of the abdomen, which showed a large mass in the right lobe of the liver. Investigation of the mass using MRI of the abdomen and a CT guided biopsy revealed a moderately differentiated adenocarcinoma, which was negative for prostate markers but favored a biliary or pancreatic origin. A subsequent CT demonstrated a mass in the tail of the pancreas, which was confirmed histologically as a high-grade adenocarcinoma, which was also negative for prostate markers.

Laboratory work done at that time showed a cancer antigen (CA) 19-9 level of 127.3 U/ml (reference range 0–35 U/ml) and a carcinoembryonic antigen (CEA) level of 2.8 ng/ml (reference range 0–5.0 ng/ml) and PSA level of 0.3 ng/ml (reference range $> 4.0$ ng/ml). Other tests, including glucose, alkaline phosphatase, transaminases, and bilirubin were within the normal range.

The patient's family history was significant for multiple cancers. His daughter was diagnosed with breast cancer at 40 years of age. His sister was also found to have breast and thyroid cancer at 40 years of age. Further pedigree analysis revealed multiple cancers including pancreatic, breast, prostate, lung, and skin cancers in multiple generations. BRCA testing done after genetic counseling revealed the presence of the mutation 6174delT which commonly occurs in BRCA2 positive Ashkenazi Jewish populations.

The patient commenced on the gemcitibine (GTX) regimen (GTX 750 mg/m$^2$ and docetaxel 30 mg/m$^2$ on days 4 and 11 in combination with capecitabine 750 mg/m$^2$ bid on days 1–14 of a 21 day cycle) [16]. Disease activity was monitored with serial CT scans of the chest, abdomen and pelvis as well as regular CA 19-9 and CEA levels. CA 19-9 remained stable between 60 and 70 U/ml and CEA levels ranged between 1 and 2 ng/ml. After 22 cycles

of GTX, the patient was found to have progression of his liver disease.

He was therefore switched to single agent irinotecan (175 mg/m$^2$, administered every 21 days) [9]. The patient's disease remained stable on this regimen for 18 months until a restaging CT scan showed progression of disease. Cetuximab (150 mg/m$^2$, administered weekly) was added to the above regimen on the basis of a wild-type KRAS [17] and he remained stable for a further 13 months when he was found to have a new hepatic lesion at interval restaging. CA 19-9 levels had also gradually risen to 1100 U/ml and CEA levels had increased to 15.5 ng/ml. Alternative treatment options were considered and he commenced on a 21 day regimen comprising MMC (8 mg/m$^2$ on day 1) and oxaliplatin (85 mg/m$^2$ on days 1 and 15). The patient developed a grade 2 hypersensitivity reaction to oxaliplatin necessitating withdrawal of the drug. As the patient had good response to single agent irinotecan in the past, he was restarted on irinotecan along with MMC. The patient remains well on this regimen and he has an electrocorticography performance status of 0, four and a half years post the initial diagnosis of metastatic pancreatic carcinoma.

## Discussion

Adenocarcinoma of the pancreas is the fourth most common cause of death from cancer in the United States and has the lowest survival rate for any solid tumor [18]. Overall 2-year survival is less than 10% [19]. At diagnosis, cases are generally divided into three categories, namely, resectable, locally advanced and metastatic. Only 15–20% of pancreatic cancers are amenable to surgical resection at the time of presentation and of these, less than 20% achieve long-term disease free survival.

The majority of patients initially present with locally advanced or metastatic pancreatic adenocarcinoma, largely because of the nonspecific symptoms and/or delay in receiving appropriate diagnostic testing. Very few patients with advanced disease have prolonged survival, regardless of treatment modality. Despite recent advances in chemotherapy and targeted biological agents for other cancers, the survival for pancreatic cancer remains bleak. The median survival for locally advanced and metastatic pancreatic cancer is less than 1 year with optimum treatment and only 3–4 months if left untreated, statistics which have not changed in many years [20].

Most pancreatic carcinomas are sporadic in origin. Risk factors include advancing age, smoking (in up to 25% of cases), diabetes mellitus, and chronic pancreatitis. Hereditary predisposition accounts for up to 10% of cases of pancreatic cancer. Inherited syndromes with an increased risk of pancreatic carcinoma include hereditary nonpolyposis colorectal cancer, familial atypical multiple mole melanoma, Peutz–Jeghers syndrome, cystic fibrosis, diabetes mellitus, and hereditary pancreatitis. In addition, it is known that carriers of certain germline mutations including BRCA2, p16, cationic trypsinogen, and STK11 also have an increased risk. Our patient has a BRCA2 germline mutation which is found in 12–17% of patients with familial pancreatic cancer [21,22]. In addition, our patient is of Ashkenazi Jewish descent; BRCA2 is thought to play a role in as many as 10% of pancreatic ductal adenocarcinomas in the Ashkenazi Jewish population [23]. Also, he was diagnosed with prostate cancer and pancreatic cancer concurrently, his BRCA2 mutation increasing the risk for both cancers.

BRCA1 and BRCA2 are tumor suppressor genes that are inherited in an autosomal dominant fashion. Mutations of these genes confer a greater lifetime risk of cancer. The spectrum of cancer susceptibility is wide, but in women in particular, the risk of breast, ovarian, peritoneal, and fallopian tube carcinomatosis is greatly increased. For example, the risk of breast cancer in a woman with a BRCA1 or BRCA2 mutation who is from kindred with multiple cases of breast and/or ovarian cancer may be up to 87% in her lifetime.

These germline mutations also increase cancer risk in men. BRCA2 is the most relevant gene in men and men with mutated BRCA2 are at significantly higher risk of male breast cancer, prostate cancer and pancreatic cancer as well as a lesser (but nevertheless increased) risk of developing buccal carcinoma, stomach cancer, melanoma of skin and carcinoma of the bile ducts, and gallbladder [24].

To date, the vast majority of the BRCA2 germline mutations associated with pancreatic cancers have been found in patients of Ashkenazi Jewish descent; the most common of such mutation, 6174delT (RR 1.68), occurs in approximately 1% of all Ashkenazi Jews and was found to be positive in our patient [25].

Germline BRCA2 mutations represent the most common inherited predisposition to pancreatic carcinoma identified to date. The estimated lifetime risk of pancreatic cancer in (male or female) carriers of BRCA2 is thought to be as high as 5%. The age of onset of pancreatic carcinoma in patients with BRCA2 mutation seems variable and no particular positive or negative prognostic features have been attributed to BRCA2 associated pancreatic cancer in studies to date.

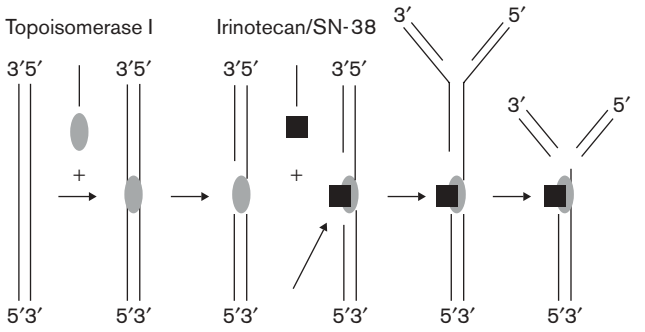
BRCA1 and BRCA2 associated breast cancers are characterized at a younger age by the onset of the disease, frequent bilateral disease, and worse histo-prognostic features. However patients with hereditary breast cancer because of BRCA2 have, overall, a similar clinical outcome when compared with age matched

sporadic breast cancer patients [26,27]. This may be because of increased genetic counseling, screening, and surveillance as well as a tendency to be steroid receptor positive. Our patient has had a prolonged survival with metastatic pancreatic carcinoma in the setting of an inherited susceptibility. From a review of the literature there is currently no data to suggest that BRCA2 associated pancreatic cancer has a different prognosis or clinical outcome from sporadic pancreatic cancer.

More than 80% of pancreatic cancers are not amenable to surgery at the time of diagnosis. Locally advanced and metastatic pancreatic cancers are essentially treated similarly, with systemic chemotherapy. Pancreatic tumors are notoriously chemoresistant and pancreatic cancer patients often have debilitating symptoms out of proportion to their tumor burden thereby limiting their tolerance to chemotherapy. In the past decade, the standard of care with regard to chemotherapy has been weekly GTX (1000 mg/m$^2$), which has been shown to have a modest advantage in both side effect profile and survival over bolus 5-FU. Median overall survival with gemcitabine is in the range of 3.7–10.7 months in comparison with 3–5 months with no treatment and 1.6–4.8 months with bolus 5-FU alone [7]. There have been numerous randomized phase III trials of cytotoxic and targeted agents alone and in combination with GTX in the past 10 years in the hope of finding a tolerable combination with improved therapeutic efficacy. A recent meta-analysis of 15 of these trials, investigating GTX based combination regimens adding a second cytotoxic agent such as a platinum analog, a fluoropyrimidine, a multitarget antifolate or topoisomerase inhibitors, showed that patients with a good initial performance status may have a statistically significant survival benefit. This benefit was principally seen in patients who received a fluoropyrimidine or a platinum analog as part of the doublet. Irinotecan in combination with GTX showed a modest improvement progression free survival but not overall survival [28,29].

Our patient presented at the age of 71 years with a dual diagnosis of prostate carcinoma and pancreatic carcinoma on a background of a significant family history of cancer. On genetic testing, he was found to have the common Ashkenazi Jewish BRCA2 mutation, 6174delT. He did not have mutated KRAS. He has done exceptionally well on chemotherapy. To date, he has received 22 cycles of docetaxel, capecitabine and GTX followed by single agent irinotecan every 3 weeks for 27 cycles, weekly cetuximab was then added to the regimen at cycle 28. His disease then remained stable for a further 13 months. MMC and oxaliplatin was then introduced but the oxaliplatin was withdrawn owing to a hypersensitivity reaction. His current treatment is MMC plus irinotecan [30]. DNA topoisomerases are nuclear enzymes responsible for the regulation of DNA topology. They are involved in basic DNA transactions during replication, transcription, and recombination. BRCA2-deficient human cells are deficient in the repair of double-strand breaks and DNA cross-links through homologous recombination. Active poisons of topoisomerase I include derivatives of CPT (Fig. 2). Our case is the first clinical piece of evidence that demonstrates an increased sensitivity to CPT-11 and a reduced topoisomerase I relaxation activity in BRCA2 associated pancreatic cancer.

**Fig. 2**




Mechanism of action of irinotecan.

It is not known whether the patient's BRCA2 status, specific chemotherapy combinations used, or an interaction between them have influenced his dramatic clinical response and good performance status. There is some evidence linking BRCA2 mutations with sensitivity to intercalating agents and one of the few reports of prolonged survival of a patient with metastatic pancreatic cancer is one in which a BRCA2 mutation was present and a MMC based regimen was used [31]. Certainly if this were truly the case, future therapy for patients with BRCA2 mutation associated pancreatic cancer could look forward to treatments tailored toward their specific disease.

We believe that it was important to describe this case of a meaningful clinical response to second-line CPT-11, third-line CPT-11 plus cetuximab and now fourth-line with CPT-11 plus MMC in a patient who carried a BRCA2 mutation. This case shows that patients with metastatic pancreatic carcinoma and BRCA2 mutations may have disease that is biologically more chemosensitive and consequently prolong survival despite prognostically unfavorable disease. Although the BRCA2 mutation is relatively rare in patients with pancreatic cancer (less than 10%), our experience with this patient suggests that irinotecan might be a useful therapeutic option in selected patients. Further studies are needed to assess the impact of irinotecan on BRCA2 mutation carriers with pancreatic cancer.

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