

Long-term complete remission of two patients with synchronous liver metastasis from pancreatic cancer and underlying BRCA-2 mutation

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has a known poor prognosis. For a select group, those with BRCA mutations, frontline platinum-based therapy and poly (ADP-ribose) polymerase inhibitors are options that can potentially lead to survival benefit.

Patients and methods: we present 2 cases of patients with BRCA-mutated pancreatic cancer with liver metastases that achieved a remarkable long-term complete remission on platinum-based chemotherapy.

Conclusion: Germline testing for BRCA is important in PDAC because it influences treatment choices that impact survival. Complete responses with chemotherapy alone are rarely observed in metastatic PDAC, but may be seen upon treatment with platinum-based therapy. (*Acta gastroenterol. belg.*, 2024, 87, 521-523).

Keywords: BRCA mutation, liver metastasis, pancreatic carcinoma, case study.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, with a 5-year survival rate of less than 10%, usually due to late-stage diagnosis and chemoresistance (1,2).

Approximately 10% of PDAC cases are associated with a hereditary predisposition and a pathogenic BRCA2 mutation is found in up to 2% of patients while BRCA1 mutation in 1% or less (3). Interestingly, recent data published by the Pancreatic Cancer Case-Control Consortium (PanC4) showed that the heritability of PDAC might be more than twice as high, reaching 21.2% (4).

The cornerstone of therapy for inoperable or metastatic PDAC remains chemotherapy. For patients with BRCA mutations, frontline platinum-based therapy can potentially lead to increased overall survival (OS) (5).

We present 2 patients with BRCA-mutated pancreatic cancer (PC) with liver metastases that achieved a remarkable long-term complete remission (CR) on chemotherapy. Both patients provided their informed consent for publication.

Case 1

A 45-year old man presented with abdominal pain and jaundice. His mother had a history of ovarian cancer. Abdominal computed tomography (CT) showed a tumor in the head of the pancreas (Figure 1).



Figure 1. — Pancreas tumor.

Biopsies of a liver lesion in segment III showed a well differentiated adenocarcinoma, compatible with a metastasis from pancreatic origin. Patient was started on Folfirinox (85mg/m² oxaliplatin, 180 mg/m² irinotecan, 400 mg/m² folinic acid, 400mg/m² bolus and 2400 mg/m² > 46h 5-FU).

After 12 cycles, chemotherapy was stopped upon radiologic CR and normalization of CA 19.9.

Germline test showed a BRCA2 mutation, BRCA2_c.4935delA (p.Glu164fs).

He was included in a phase I study with Olaparib (PARP inhibitor) + Tamoxifen five months later, still in CR radiologically. Because of episodes of cholangitis requiring several endoscopic stent replacements, Olaparib had to be stopped after ten months. The patient subsequently underwent pancreaticoduodenectomy and resection of segment III. Final pathological report showed no residual tumor.

He is still in CR, eight years after stop of Olaparib.

Case 2

A 35-year old woman presented with a 5cm mass in the head of the pancreas (Figure 2 D) and liver metastases in segments III, IV and V. (Figure 2 A, B and C)

Family history was positive for prostate (father, 60 years of age) and breast cancer (paternal grandmother, 60 years of age).

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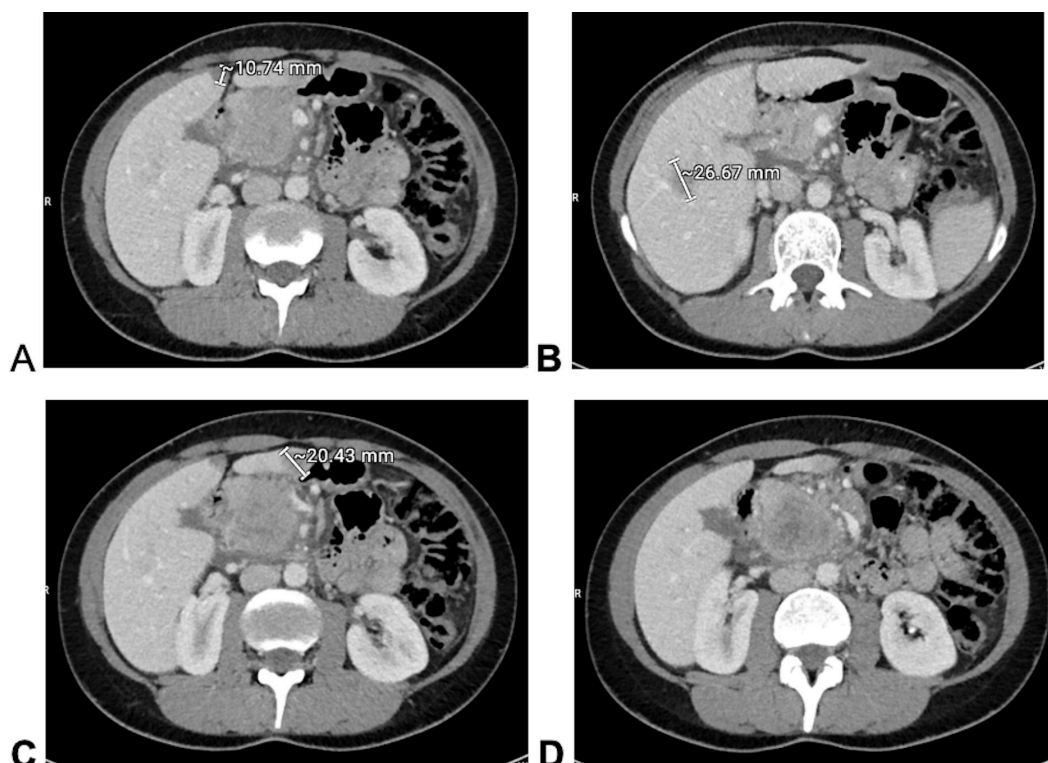


Figure 2. — Metastases segment IV (A), V (B) and III (C) ; D primary tumor.

Biopsies showed a poorly differentiated adenosquamous carcinoma of the pancreas. The patient started palliative chemotherapy Folfirinox q2w. After 10 cycles, radiologically CR was documented and therapy was downgraded to modified de Gramont. After one year of maintenance, because of lasting CR, treatment was stopped. Genetic analysis showed a pathogenic BRCA2 mutation c.8243G>A, p.(Gly2748Asp).

The patient remains in CR, without surgery, six and a half years after stop therapy.

Discussion

PDAC is the fourth leading cause of cancer-related death and particularly refractory to treatment (1,2,6).

Of all pancreatic cancers, 95% are adenocarcinomas of the ductal epithelium (7). Adenosquamous carcinoma (ASC) of the pancreas is a rare variant, with an incidence of 1-4% of all pancreatic malignancies and associated with a worse prognosis (8).

Families are considered to have familial pancreatic cancer (FPC) when two or more first-degree relatives (FDRs) have PC (3). The risk on developing PDAC increases with the number of affected FDR, being higher in those who carry a pathogenic germline variant (4). These germline variants are closely related to other tumors and this should be kept in mind when gathering familial history.

The last update of the NCCN guidelines recommends genetic counseling and testing to all patients diagnosed with PDAC since deleterious variants in the known pancreatic cancer susceptibility genes account for ~10-20% of familial clustering of PC. (3,4,6,9).

BRCA1 and BRCA2 are the most common known genetic mutations involved in FPC. The relative risk for PC is 3.1 in BRCA 1 and 6.6 in BRCA2 mutation carriers (9). These tumor suppressor genes are involved in the process of homologous recombination repair (HRR), which mediates double-stranded DNA breaks. Patients with germline BRCA mutations exhibit an impaired ability to repair these breaks.

There is accumulating evidence of increased sensitivity to platinum-based therapy and PARP inhibitors in BRCA-associated PDAC (10-12). Platinum-based drugs bind directly to DNA, causing DNA double-strand breaks, which are not repaired in case of an abnormally functioning BRCA gene (7). Normally, when a double-strand DNA break is detected, it is followed by HRR, to restore the original DNA sequence. Nuclear enzyme poly (ADP-ribose) polymerase (PARP) is responsible for detecting DNA damage and facilitating its repair. Specifically PARP1 binds to and repairs DNA breaks (13). This biologic phenomenon was the basis for the phase III POLO trial.

Seven and a half % of screened patients for this trial had a germline *BRCA* mutation. One hundred fifty four out of 247 patients underwent randomization between placebo or maintenance Olaparib when no progression during first-line platinum-based chemotherapy was seen (11). The choice of platinum-based first line chemotherapy was supported by several observations, including one in 7 patients with stage III and IV BRCA mutated PC, showing superior OS for those treated with platinum vs those treated with non-platinum chemotherapies (22 vs 9 months; $P=0.039$) (5, 14).

ASCO guidelines recommend that patients who received first-line platinum-based chemotherapy without disease progression for at least 16 weeks, continue treatment with chemotherapy or PARP inhibitor Olaparib because of the results of the aforementioned phase III POLO RCT (10). Progression free survival was significantly better for patients assigned to Olaparib compared to placebo (7,4 months v 3,8 months; hazard ratio, 0,53 (95% CI, 0,35 to 0,82; $P=0,004$) (11). There were no significant differences between both groups for OS, because cross-over was allowed. Interestingly, median OS was longer for patients who had received > 6 months versus $\leq$ 6 months of first-line chemotherapy (olaparib: 32.5 months; 95% CI, 17.2 to 43.6 months; placebo: 20.6 months; 95% CI, 16.1 to 27.2 months versus olaparib: 17.0 months; 95% CI, 11.7 to 19.2 months; placebo: 15.0 months; 95% CI, 10.6 to 21.1 months).

The POLO trial demonstrated that not all patients with a germline BRCA mutation benefit equally from platinum-based chemotherapy. Our cases are illustrations of exceptional responses, something that has not been described often before and emphasizes the importance of exposing patients with BRCA mutated PC to platinum-based therapy (5). Both our cases are BRCA2 mutated. In a cohort of patients with germline BRCA and pancreatic cancer, BRCA2 were associated with better outcomes compared with BRCA1. There was an enhanced benefit from platinum-based therapies and resection in BRCA2 compared to BRCA1 carriers (15).

We admit that we cannot link with certainty the spectacular outcome in our two cases to the use of platinum-based therapy solely and therefore the role of other factors influencing the grade and type of the response to therapy should also be assessed.

In conclusion, complete responses with chemotherapy alone are rarely observed in metastatic PDAC. These 2 cases have long-term clinical and/or pathological CR upon treatment with platinum-based chemotherapy in metastatic BRCA mutated pancreatic carcinoma. Especially in young patients in whom familial cancer is suspected, genetic testing should be offered, because it is possible to have a CR on platinum. Not all patients with BRCA-mutated PDAC have similar responses however. Other factors beyond germline status, like the specific variant, tumor biology, treatment regimen or combination may also partly explain these unique results.

Special cases like these need to be shared to enable deeper investigations.

Conflict of interest statement

The authors declare no conflict of interest

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