

Pancreatic Ductal Adenocarcinoma Harboring Germline BRCA 2 Mutation, A Case Report and Review of The Literature

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Abstract

Introduction: Despite recent advances in the diagnosis and treatment of pancreatic ductal adenocarcinoma (PDAC) the prognosis of this tumor remains dismal. It is estimated that 5-10% of all PDAC patients harbor a germline BRCA-1 or BRCA-2 mutation. There is some evidence that BRCA-mutated PDAC cases respond to chemotherapy regimens based on platinum derivate and cross linking agents.

Case report: Here we present a case of metastatic PDAC in a 41-year-old BRCA2 germline mutation carrier. The patient had a favorable response to systemic treatment, including a partial response even to the third line cisplatin monotherapy administered with palliative intent.

Discussion: PDAC associated with BRCA mutation represents a special disease entity. Platinum derivates and cross linking agents should be considered even in the advanced palliative setting in these patients.

Keywords: Pancreatic cancer; BRCA; Mutation; Platinum; Chemotherapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most challenging malignant disorders. Up to 80% of patients present with unresectable or metastatic disease that is associated with very poor prognosis. Cytotoxic chemotherapy remains the cornerstone of the treatment in the locally advanced and metastatic PDAC. Even though new chemotherapy regimen such as FOLFIRINOX (oxaliplatin, irinotecan, and 5-fluorouracil) or the combination of gemcitabine and nab-paclitaxel have been introduced in the first line treatment, the median overall survival (OS) in the setting of locally advanced and metastatic disease doesn't exceed 11 months [1].

The toxicity profile is of paramount importance in the palliative setting. Compared to gemcitabine monotherapy, FOLFIRINOX is associated with higher rates of grade 3 and 4 toxicities, including febrile neutropenia (5.4%), diarrhea (12.7%), and sensory neuropathy (9.0%). FOLFIRINOX is regarded as a suitable regimen for patients younger than 76 years, with good performance status (ECOG 0 or 1), no cardiac ischemia and normal bilirubin levels. Different modifications of FOLFIRINOX that have been evaluated in various clinical trials showed improved safety with maintained efficacy in the treatment of PDAC, becoming a reasonable alternative to be offered to the patients.

Based on the results of MPACT trial novel agent nanoparticle albumin-bound (nab)-paclitaxel in combination with gemcitabine became a new treatment option for patients with metastatic PDAC [2]. A favorable toxicity profile, including grade \geq 3 neutropenia (38%),

fatigue (17%), and neuropathy (17%), has made this combination a good alternative to FOLFIRINOX.

Identification of predictive and prognostic biomarkers is essential for individualized tailored therapy. However, no predictive and prognostic biomarkers have been identified for the metastatic or locally advanced disease so far. Nevertheless, 5-10% of PDAC patients with pancreatic cancer harbor BRCA1 or BRCA2 mutation [3]. BRCAmutated PDAC represents a specific disease entity characterized by a more favorable prognosis, probably due to the chemosensitivity, specifically to platinum derivates. Moreover, new treatment possibilities of targeted therapy, poly ADP ribose polymerase (PARP) inhibitors, are being currently explored in clinical trials. However, the predictive role of the BRCA mutation hasn't yet been prospectively established in PDAC.

We present a case report of a patient with metastatic BRCA2mutated PDAC who had good response to combination of gemcitabine and nab-paclitaxel in the second line setting. Moreover, the third line treatment with cisplatin monotherapy was also effective and welltolerated.

Case Description

A 41-year-old man diagnosed with PDAC with no other comorbidities was referred to our institution in May 2014. CT scan showed a primary tumor of the size 28×22 mm in the tail of the pancreas invading the spleen and the splenic artery, multiple liver metastases sizing up to 26 mm and infiltration of the right lower lung lobe. Endoscopic ultrasound guided fine needle aspiration biopsy confirmed poorly differentiated PDAC (grade 3). Bronchoscopy was performed to exclude synchronous primary lung cancer. The disease

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extent was classified as cT4cN1cM1; stage IV according to the TNM Classification of Malignant Tumors (7th edition).

The patient was also diagnosed with deep venous thrombosis of the left popliteal and superficial femoral vein at the presentation and started anticoagulation treatment with low molecular weight heparin. Laboratory results showed only mildly increased activity of alkaline phosphatase (10.29 μ kat/l) and gamma-glutamyl transferase (15.31 μ kal/l). Value of carbohydrate antigen (CA) 19-9 was extremely elevated (>10 000 kIU/l).

A combined modified (m)FOLFIRINOX regimen (Irinotecan 135 mg/m²/90 min, Oxaliplatin 85 mg/m²/120 min, Folinic acid 400 mg/m²/120 min, 5-FU 300 mg/m² IV (intravenous) bolus, then 2400 mg/m² continuous intravenous infusion over 46 hours) was chosen for the first line treatment with regard to a good performance status (PS1), age of the patient and normal bilirubin levels.

Seven cycles of mFOLFIRINOX were administered during three months (June 2014 to September 2014) along with anti-emetic medication consisting of intravenous dexamethasone (16 mg), and palonosetrone (0.25 mg). The treatment was well tolerated, and no severe adverse events of grade 3 and/or 4 were recorded. There was no need for nutritional intervention or changes in analgesic medication. Values of CA 19-9 decreased to 2574 kIU/l (Figure 1). Control CT in September 2014 showed regression of visceral metastases (complete disappearance of lung metastases as well as partial regression of liver metastases were detected in shoulder blades, ribs, spinal vertebra and sacrum which were considered a progression of the disease.



Figure 1: CA19-9 levels during the patient treatment.

The patient underwent a second line of combination chemotherapy consisting of gemcitabine (1000 mg/m²/30 min day 1,8,15) and nabpaclitaxel (175 mg/m²/30 min day 1,8,15) administered in 4-week cycles starting in October 2014. Intravenous bisphosphonates were also initiated. Neutropenia grade 3 and thrombocytopenia grade 2 (according to NCI-CTC v.3) occurred after the third cycle. The regimen was changed to biweekly modification of gemcitabine (1000 mg/m2/30 min and nab-paclitaxel (175 mg/m²/30 min) [4] There has been continuous decline of CA 19-9 (Figure 1; 95.7 kIU/l; 3/2/2015) and improvement of liver tests to physiological values for 9 months since the date of diagnosis. Moreover, no severe adverse events grade 3 or 4 occurred, including hematological toxicity in the biweekly modification of this regimen. Control CT scan in March 2015 confirmed stable disease. The treatment was further well tolerated. The patient could spend his time with his hobbies such as hiking and skiing. Nevertheless, there was a rise of CA 19-9 since April 2015 reaching up to 9783 kIU/l in May 2015 (Figure 1). The combination treatment of nab-paclitaxel and Gemcitabine was terminated on April 24th 2015 and control CT scan showed multiple diffuse hypodensed areas with postcontrast saturation and one hyperdensed lesion confirming the progression of liver metastases in May 2015. Third line treatment was indicated with regard to good performance status of the patient (WHO performance status 1) and his tolerability of the previous treatments. Cisplatin monotherapy was selected because BRCA mutation was suspected, considering the young age of the patient and sensitivity of the disease to prior chemotherapy. On June 5th 2015 the patient started the third line of palliative chemotherapy of single-agent cisplatin administered in biweekly intervals (60 mg/m²). The treatment was tolerated well; there has been only hematological toxicity, mainly grade 3 neutropenia and grade 2 thrombocytopenia, for which some of the cycles had to be postponed. The patient started feeling well again and began with his active hobbies. CA 19-9 started declining again to the nadir value of 1593 kIU/l in September 2015. Control CT confirmed partial regression of liver metastases and the lesion in the tail of pancreas. The response to the treatment lasted till December 2015 when the level of CA 19-9 began to rise again. In January 2016 germline BRCA 2 mutation (c.7910_7914delCCTTT, p Phe2638Ter) was discoverd. Control CT scan on January 13th 2016 revealed new progression of liver metastases and peritoneal carcinomatosis. As there was no clinical trial available for PDAC patients with BRCA 2 mutation and the patient still had a good performance status, 4th line of palliative treatment with 5-fluorouracil was initiated. Nevertheless, the patient condition was deteriorating. The patient complained of abdominal pain for which opioids and regular paracentesis were initiated. CT scan in March 2016 showed progression of liver, pancreatic lesions and bone metastases. The chemotherapy treatment is terminated and patient is indicated for symptomatic treatment.

The patient died on April 28th 2016 at home in the middle of his family after 24 months after starting the systemic anticancer treatment and almost 20 months of active life.

Discussion

In the developed countries, the incidence of PDAC is 12 cases per 100 000 inhabitants per year [5]. While most of the PDAC cases are sporadic, up to 10% of PDAC have a hereditary cause [6]. Hereditary PDAC has been associated with several germ-line mutations, primarily in the tumor suppressor genes such as p16 (familial atypical melanoma mole syndrome [7], STK11 (Peutz-Jeghers syndrome [8], hMLH1 (hereditary nonpolyposis colon cancer [9], FANCC [10,11], and PRSS1 (hereditary pancreatitis) [12]. Nevertheless, the most predominant mutations identified in patients with hereditary PDAC are the germline mutations of BRCA1 and BRCA2 genes, the breast cancer early onset tumor suppressor genes [13]. Both BRCA1 and BRCA2 genes involved in the repair of DNA double strand breaks through homologous recombination pathway. The BRCA1 or BRCA2 deficient cells accumulate double strand breaks resulting in genomic instability and malignant transformation. The mutations of BRCA 1/BRCA 2 predispose to breast cancer, ovarian cancer and also to PDAC. The risk of PDAC by age 70 in BRCA 1/BRCA2 carriers is ranging between 1.16 to 4.1% [14]. Some studies suggest that there is a similar risk for both BRCA1 and BRCA2 carriers; however, most reports noted increased risk of PDAC mainly in the BRCA2 carriers [14,15].

According to the available data, BRCA deficient PDAC represents an entity with unique biology and clinical outcome. The young age of the patients and chemosensitivity of the disease are thought to be the primary factors responsible for a more favorable prognosis [16]. The young onset of the disease in the families with cancer history should arise the suspicion of BRCA mutation. Golan et al reported a ten year age difference compared to unselected population, with mean age at diagnosis being 60.3 years in a cohort of 71 patients with BRCA mutated PDAC [16].

Clinical data of patients with BRCA deficient ovarian and breast cancer show higher response rates to treatment with DNA crosslinking agents such as platinum derivates and mitomycin C [17]. Similar observations have been made in case of BRCA mutated PDAC. However, the published experience with relatively rare patients with BRCA-mutated PDAC is limited to case reports or case series. Sonneblick et al have published a case report of a patient with BRCA 2 mutated PDAC and complete response to second line cisplatin [18]. Partial response of BRCA2 mutated PDAC to the third line of combination chemotherapy mitomycin C plus capecitabine has been reported by Chalasani et al. [19]. Sharma et al. described three cases of BRCA mutated PDAC responding to platinum based chemotherapy. Two patients have responded to oxaliplatin in combination regimen FOLFIRINOX administered in neoadjuvant setting, and one patient had a partial response after first line chemotherapy gemcitabine plus cisplatin [20]. Retrospective analysis by Tran et al. of five patients with BRCA mutated PDAC from Ontario Pancreatic Cancer Study and pharmacy database supports previously reported effectiveness of platinum- based chemotherapy in BRCA-mutated PDAC [21]. Larger series of BRCA mutated pancreatic cancer have been reported from Memorial Sloan-Kettering Cancer Center and by Golan et al. [22,16] The Memorial Sloan-Kettering Cancer Center series reported six cases of patients treated with platinum-based combination and medium OS 27, 6 months, including one patient with complete response. Golan et al. collected data from a clinical database of 3 medical institutions in Canada and Israel. They performed retrospective evaluation of 43 patients diagnosed with BRCA1 or BRCA2 associated stage III and IV PDAC. Patients treated with regimens containing platinum achieved 13 months longer median overall survival compared to those who did not receive platinum (median 22 vs. 9 months).

Although more or less anecdotal, these results support the hypothesis of sensitivity of BRCA-mutated PDAC to platinum-based regimen and cross-linking agents leading to the utilization of these drugs in the treatment. However, the numbers of patients reported are still very small, different doses of platinum and different regimens in various setting have been used.

No standard schedule of platinum derivates or cross-linking agents has so far been prospectively established in the treatment of BRCA deficient PDAC.

The role of PARP inhibitors in the treatment of the BRCA-mutated PDAC is currently being investigated in the ongoing phase II clinical trials. Although studies with platinum compounds or alkylating agents lack the commercial incentive that is behind the trials of PARP inhibitors, the evaluation, prospective or retrospective, of the efficacy of these commonly available agents in rare cases of BRCA-mutated PDAC are not of less importance.

The present case report is consistent with the previously published data, with the patient being diagnosed with PDAC at young age and the survival reaching 24 months despite the presence of massive

metastatic spread at the time of diagnosis. The reported median overall survival of metastatic PDAC treated with the most effective chemotherapy regimen FOLFIRINOX does not surpass 12 months.

The favorable outcome in the present case was associated with a good response to combination chemotherapy regimens not only in the first and second line, but even to the cisplatin monotherapy in the third-line of treatment administered with palliative intent. To the best of our knowledge this is the first report of platinum efficacy in the third line setting. This case report also illustrates a favorable safety profile of the administered regimens preserving a good quality life. As indicated above, the published experience on outcome of patients with BRCA-mutated PDAC is limited to case reports or small case series. Moreover, a prospective study would be difficult to organize because of the rarity of this presentation, difficulty to find funding for a trial using generic drugs or ethical considerations, so retrospective data from sources like a present case report currently are and probably remain the only source of information that would guide the management of a rare patient with these tumors.

In conclusion, BRCA-mutated PDAC is a relatively rare, but clinical important entity with the need of an individualized therapeutic approach. While the role of targeted therapies especially PARP is under investigation, it should not be forgotten that platinum compounds or alkylating also represent a sort of targeted treatment for these patients that is widely available at the present time.

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