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Successful multidisciplinary treatment of pancreatic cancer with a BRCA2 mutation: A case report

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Abstract

Background: In this article, we present a BRCA2 mutation positive pancreatic cancer case treated by combined (surgical and systemic) methods.

Case presentation: For than 4 years after the initial diagnosis, the patient was treated by different methods. After pancreatic cancer resection and 3 courses of the adjuvant treatment with Capecitabine and Gemcitabine, the patient received 12 cycles of palliative 1st line chemotherapy with FOLFIRINOX for 6 months and complete response (CR) was achieved. The FOLFIRINOX regimen was restarted and administered for 12 cycles after 11 months of complete response. Because BRCA2 gene mutation was detected, treatment with PARP inhibitor Olaparib was administered for 18 months (the duration of partial response) until a control MRI scan showed progression. 2nd line palliative chemotherapy with XELOX scheme was administered for 10 months. During chemotherapy treatment multiple surgeries and local treatment of metastases were performed: resection of liver metastases, bilateral ovariectomy and the local ablation of the liver metastases. Local treatment helped to reduce the progression of the disease and delayed the symptoms caused by metastases. At the moment the patient is receiving Gemcitabine and nab-paclitaxel due to disease progression. Different treatment modalities have been used and helped to achieve such a long survival for a pancreatic cancer patient with a BRCA2 mutation (OS is 54 months).

Keywords

Pancreatic cancer; Multidisciplinary approach; Surgery; Histology; BRCA mutation.

Introduction

During the new era of treatment possibilities, Pancreatic Cancer (PC) is still a challenge for clinicians all over the world. Most cases are diagnosed in an advanced stage when only symptomatic surgery or

palliative chemotherapy can prolong survival and reduce symptoms. Due to late diagnostics and increasing risk factors of modern society which are smoking, obesity, alcohol consumption and chemical exposure the survival rate of PC is still one of the lowest among all cancer types [1,2]. In WHO projection it is shown that in the year 2060 the mortality due to pancreatic cancer will be twice as high as it is today [3].

Pancreatic cancer is a heterogeneous group of tumors which encompasses intertumor and intratumor heterogeneity at the histological level [4]. The neoplastic process can occur in the exocrine or endocrine tissue of the pancreas. The most common form of PC is pancreatic ductal adenocarcinoma (~90% of all pancreatic neoplasms) [5]. Other exocrine cancers are: adenosquamous, squamous, acinar cell carcinomas, etc. Pancreatic neuroendocrine tumors (PanNET) develop from pancreas endocrine cells. PanNET illustrates <5% of all pancreatic malignancies [6].

According to the literature, pancreatic cancer is diagnosed in 3-10% of people whose family members have been diagnosed with pancreatic cancer. About 10-20% of adenocarcinomas can be hereditary [7]. Pancreatic cancer susceptibility genes are ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53. The risk of developing pancreatic cancer is 5-10% for BRCA2 gene carriers [8]. It is considered that high–risk patients are individuals who have 5% or higher risk to get PC in their lifetime while in the general population the risk is 1.3% [9] [10]. It is recognized that tumor suppressor genes BRCA1 and BRCA2 play a key role in DNA damage repair through the homologous recombination repair pathway and are the most common genes involved in causing heredity pancreatic cancer [11,12].

Both BRCA1 and BRCA2 are proteins involved in DNA double strand break repair by Homologous Recombination (HR). Loss of the functional fidelity of these proteins can lead to HR Deficiency (HRD) and when present in the tumor, interventions inducing DNA double strand breaks can be differentially more lethal to the cancer cell [13].

Surgery, radiotherapy, and chemotherapy are often combined to seek the best treatment outcomes for PC. Most of the time PC is in an advanced stage at the time of diagnosis when surgery is no longer a truly curative treatment. This is the reason why a molecular characterization of PC is the future of diagnostic and treatment modalities. Knowledge of the key factors of carcinogenesis and therapeutical targets is needed to provide better survival rates [4]. For example, more than 8% of patients with sporadic PC can have BRCA mutations and could get a benefit of treatment with platinum-based chemotherapy and PARP inhibitor [14]. There are still mixed results which clinical features can occur in BRCA-positive PC population, but multiple cohort studies have shown that these patients are diagnosed with PC earlier than patients without germ line mutations [15]. The cohort study including 71 BRCA-positive PC patients has shown that better prognosis is related with BRCA mutation [16]. One of the factors that may lead to a better prognosis in the BRCA positive population is an increased susceptibility to treatment with platinum-based chemotherapy [17].

The identification of prognostic and predictive markers and developing of a molecular targeted therapies supposed to be the future direction for PC treatment together with a multidisciplinary approach and earlier diagnostics.

In this article, we present a BRCA2 mutation positive pancreatic cancer case treated by combined treatment (surgical and systemic) methods.

Case Presentation

67-year-old female patient complained of abdominal pain, nausea provoked by food ingestion and weight loss in the year 2018. Those symptoms first appeared a couple of years before the cancer diagnosis and were intensifying until treatment stated. The patient had familial cancer history: mother was diagnosed with cervical cancer, maternal aunt had unknown gynecological cancer, patient's daughter and son – *BRCA2* carriers (daughter had hysterectomy and ovariectomy). The patient The MRI scan showed a 4,1 x 3,6 cm heterogeneous structure with cystic components in pancreatic tail – probable neuroendocrine tumor (NET) or cystadenocarcinoma. Further CT scan showed a multicystic pancreatic tail tumor, adjacent to posterior gastric wall, left perirenal fascia, and infiltration spreading towards the splenic hilum. No signs of distant metastases (MTS) were found. The case was discussed during Multi-Disciplinary Team (MDT) meeting and distal pancreatectomy was proposed.

During the initial surgery, the upper midline incision was made. After mobilizing the stomach, a polycystic tumor of pancreatic tail was exposed. The tumor was 7 x 7 x 5 cm in size, with multiple septa and walls up to 5 mm thick, penetrating the gastric wall, left adrenal gland and left perirenal fat capsule, and spreading towards the splenic hilum. The left colonic flexure with spleen, pancreatic tail, left adrenal gland and perirenal fat capsule were mobilized and partial resection of the gastric posterior wall was performed. The tumor was separated from the surrounding tissue. Then careful dissection of the common hepatic artery, splenic artery and celiac trunk was carried out, removing surrounding lymph nodes. The pancreas was resected, and the specimen was removed en bloc with the left adrenal gland, left perirenal fat capsule, spleen, and part of the posterior gastric wall. The proximal edge of the specimen was sent for intraoperative frozen section consultation which showed no tumor signs at the level of resection. Lastly, the pancreatic stump was closed, and surgical drains were placed near the pancreatic stump and in the left subdiaphragmatic space. Postoperatively the patient was observed in the Intensive Care Unit (ICU) for 5 days. Further postoperative period was uneventful, with the patient discharged on 12th postoperative day.

The final histopathological result was moderately differentiated G2 mucinous cystadenocarcinoma of pancreas pT3 pN1 M0 (tumor found in one-third of lymph nodes, surrounding lower mesenteric vein) (Figure 1) and adjuvant chemotherapy was planned 4 weeks after surgery. The patient received 3 cycles of Capecitabine and Gemcitabine as adjuvant chemotherapy at Vilnius University Hospital Santaros Klinikos.

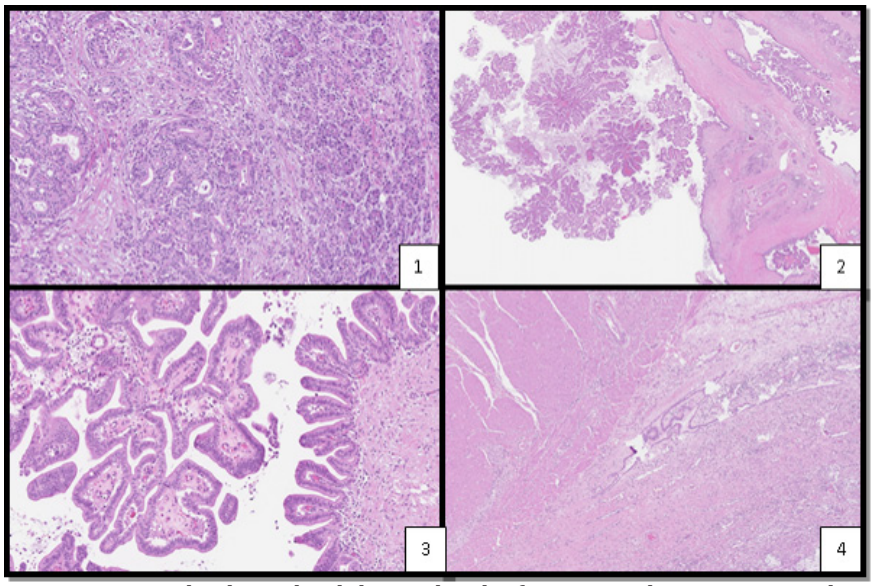

Figure 1: Tumor in pancreas displays glandular and cribriform growth pattern in a desmoplastic stroma. (x100)
2. Tumor displays branching papillary structures in cystic spaces. (x10)
3. Higher magnification of simple papillae lining cystic spaces and complex branching papillae extending into the lumen of the cyst. (x100)
4. Tumor infiltrating the subserosal layer of the stomach wall without infiltration of the muscular layer. (x40)

6 weeks after initial surgery a routine ultrasound of the abdominal cavity showed a 0,6 cm cyst in S6 segment of liver and 1,4 cm hypoechogenic lesion of S8 segment-probable cavernous hemangioma or MTS. MRI scan was performed, which clarified two lesions of liver S6 segment (1,3 cm and 0,6 cm in diameter), with the larger lesion structurally similar to the initial tumor. After the MDT meeting, it was decided to perform an atypical resection of the liver. The second surgery was performed 3 months after the distal pancreatic resection. Upper midline incision was performed with the incision continued to the right side. A lesion on the visceral surface of S6 segment of the liver was identified and verified with intraoperative ultrasound. Further exploration of the abdominal cavity was unremarkable except for a 3 mm whitish nodule on the surface of the S7 segment of the liver. It was excised and sent for intraoperative frozen section consultation which confirmed MTS. The liver was mobilized, the S6 lesion was excised, and thorough hemostasis was performed. The postoperative period was normal with the patient discharged on 5th postoperative day. One month after the surgery an abdominal MRI showed a 1.2 cm lesion in S4 and multiple lesions in the liver up to 0.6 cm.

The patient received 12 cycles of palliative 1st line chemotherapy with FOLFIRINOX at the National Cancer Institute of Lithuania (NCI). Despite mild hematological toxicity and mild signs of peripheral neuropathy chemotherapy was tolerated satisfactorily with complete radiological response. Intermediate control (liver MRI, cancer biomarkers) showed positive dynamics. Due to disease progression in the liver, MDT recommended restarting FOLFIRINOX regimen after 11 months of Complete Response (CR). 12 courses of FOLFIRINOX regiment were administered.

The final results of genetic analysis (Foundation One research) showed gene alterations: *BRCA2 E1550*, KRAS G12D* and *TP53* splice site *673-2A>G*. Microsatellite status and Tumor Mutational Burden-could not be determined. Olaparib was recommended as the best treatment option for cystadenocarcinoma

tumor type of our case.

After the good response on platinum-based chemotherapy and based on the newly received information from tissue analyses of the *BRCA2* gene mutation, maintenance with PARP inhibitor Olaparib (300 mg 2 twice per day) was recommended. Olaparib was available through compassionate use program at NCI. During the systemic treatment with Olaparib, ovarian removal was performed according to MRI findings and detection of *BRCA2* mutation. Laparotomy, bilateral adnexectomy and omentum biopsy were done. After the lower midline incision, exploration of the abdominal cavity was unremarkable. A bilateral adnexectomy was carried out, a biopsy of the omentum was taken, and the abdominal wall was closed. Postoperative period was normal with the patient discharged on 6th postoperative day. Histopathology results showed bilateral MTS in the ovaries, intact Fallopian tubes, and no MTS in the omentum (Figure 2).

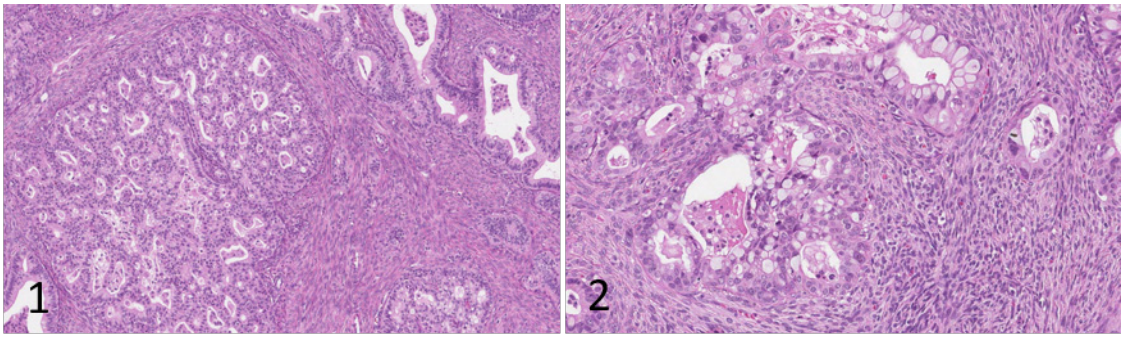

Figure 2: 1. Tumor displays glandular and cribriform growth pattern in ovarian cellular stroma. (x100).
2. Tumor structures are composed of atypical columnar epithelium and mucinous epithelium with focally abundant goblet cells. Tumor cells show minimal nuclear atypia and mitotic figures. (x200).

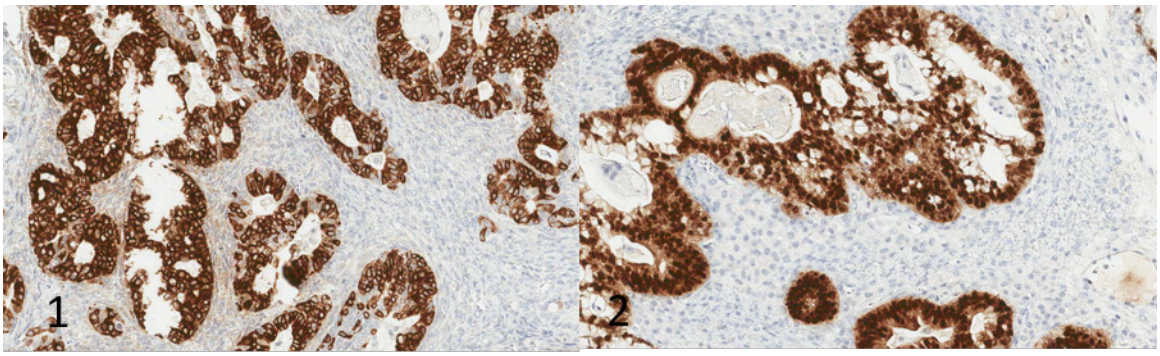

Figure 3: 1. Tumor cells show diffuse positive nuclear CDX2 staining. (x200)
2. Tumor cells show diffuse positive cytoplasmic MUC5 staining. (x200)

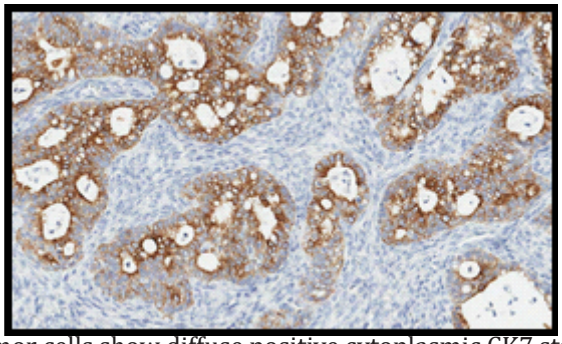

Figure 4: Tumor cells show diffuse positive cytoplasmic CK7 staining. (x200).

An immunohistochemical evaluation was performed: EMA: 100% (+++) cytoplasmic reaction. CK7 ir MUC5: 75% (++/+++) cytoplasmic reaction. CDX2: 90% (++/+++) nuclear reaction (figure 3). SMAD4, CK20: negative reaction. The combination of the three immunohistochemical markers CDX2 + CK7 + MUC5 is most consistent with pancreatic carcinoma (vs. colon, etc.) (Figure 4).

After ovarian surgery, MDT recommended to continuing Olaparib since cysts in the ovaries have been observed radiologically for a long time without clinical symptoms. Microwave ablation of the liver MTS was also performed. A 1 month later, the patient was admitted to the emergency department with a fever and abdominal pain. The CT scan showed an 8,4 x 3,4 x 7,0 cm subcapsular lesion of liver – probably biloma. No signs of disease progression were identified. The patient was treated with perihepatic biloma drainage and antibiotics before being discharged on the seventh postoperative day with no complications. At the end of the year 2020, the patient was diagnosed with COVID-19 infection, with moderate symptoms of the disease, and did not need hospitalization. The patient was fully vaccinated with the COVID-19 vaccine. Olaparib was administered for 18 months till a control MRI scan showed growth of the liver S3 lesion (x3,6 times larger), multiple new superficial lesions of S7, S6, S5 and S4a up to 11 mm in size (the largest of them being S6), and a pathological 15 x 7 mm supraumbilical lesion in the m. rectus abdominis diastasis. Further PET/CT scans proved the same lesions to be metabolically active and similar to metastases (spread in the liver and peritoneum). The case was discussed by the MDT of NCI and surgical removal of all these lesions was recommended, followed by 2nd line palliative chemotherapy with the XELOX scheme.

The decision on the chemotherapy regime was based on the BRCA2 mutation. During the last surgery, an extended right subcostal incision was made, and careful adhesiolysis was carried out. Multiple lesions in the abdominal wall and cavity, described on CT, were localized and removed. A couple of small 1 mm lesions were found in the peritoneum and one of them was removed from the anterior surface of the pancreas for examination. Finally, a cholecystectomy was performed with the cystic duct and artery being ligated. The postoperative period was uneventful, and the patient was discharged on the fourth postoperative day. The final histopathology result confirmed most of the lesions being MTS, except for one lesion of the abdominal wall being a focal inflammatory reaction and no signs of tumor found in the gallbladder (Figure 5).

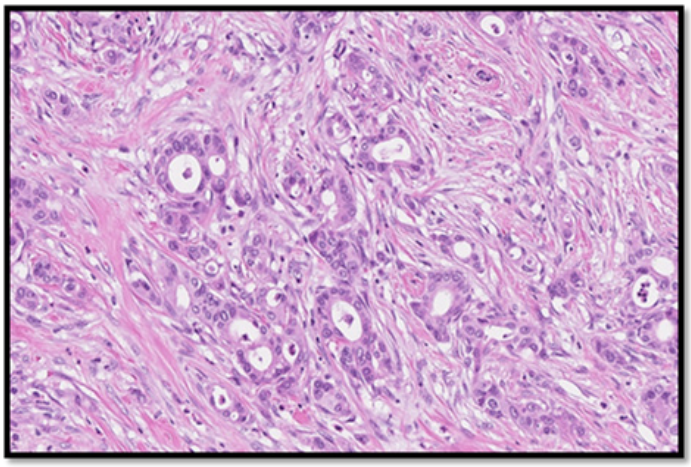

Figure 5: Histological slide stained with hematoxylin and eosin, magnification x20: the tissues of the abdominal wall are infiltrated by small glandular structures (arrows) surrounded by remarkably desmoplastic stroma (stars).

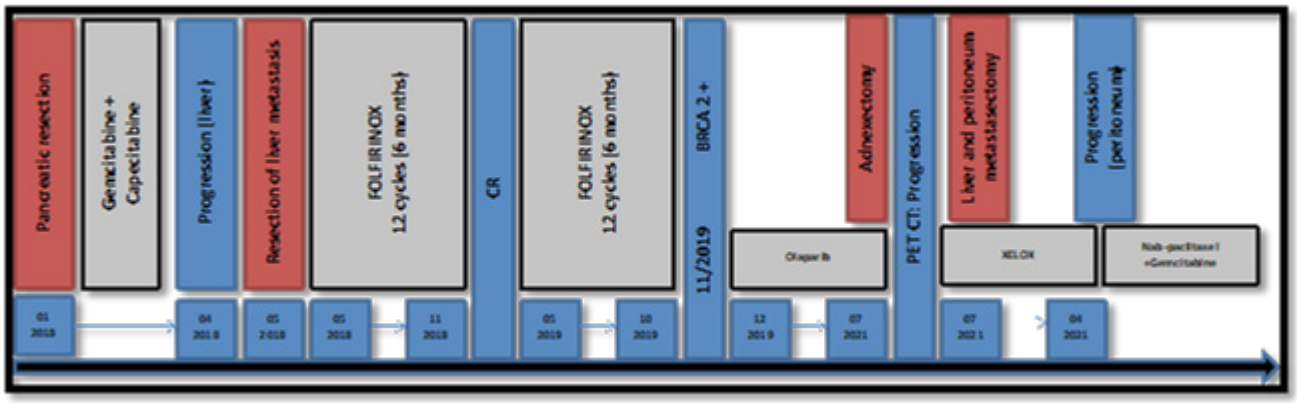

Figure 6: A case report timeline: An integrated, individualized and multidisciplinary approach.

The gland is lined with epithelium with irregular nuclei, mitoses, and eosinophilic cytoplasm. Tumor cell complexes and single cells are visible between glandular structures (HEx20).

Second line palliative treatment with XELOX was administered for 10 months and stopped due to hematological toxicity: grade 1 leucopenia and peripheral sensory neuropathy (grade 1-2 according to CTC criteria). 27 Control CT scan showed no clear evidence of the disease. Cancer biomarkers CEA and CA19-9 are currently normalized.

Currently, the progression of metastases in the peritoneum is detected. Surgical treatment options have been exhausted. Systemic treatment with nab-paclitaxel and Gemcitabine was recommended by the MDT of NCI. The patient is still physically active and her performance status is good (ECOG-1).

Discussion and Conclusions

A rare case of advanced PC with multiple metastases, which was treated with combined treatment methods, is presented in this report. In our presented case, the patient had a good response to platinum-based chemotherapy (CR after administration of FOLFIRINOX and a partial response (PR) after a repeat of FOLFIRINOX) with an additional 18 months with maintenance of Olaparib.

The 5-year survival rate of PC is still only 9% [18]. After diagnosis with PC, only 24% of people survive 1 year. This is the reason why early diagnostic methods should be invented as soon as possible. Screening of targeted groups (it could be BRCA-positive family history) is being evaluated [18]. Other germline and somatic DNA damage repair (DDR) gene mutations: PALB2, ATM, and CDK12 are also considered as targets for Olaparib [19]. A larger group of patients could get a benefit from Olaparib if more DDR gene mutations were included in diagnostics [20].

Although the frequency of germline mutations is not high in PDAC patients, their characteristics of tumors are likely to increase the benefit of platinum-based chemotherapy. In a 71-patient analysis, the median OS of patients with BRCA1 and BRCA2 mutations was 15 months and 13 months, respectively [21]. The 5-year survival rate for stage IV pancreatic cancer is 3%. The median survival for untreated advanced pancreatic cancer is 3.5 months. With active treatment, the median survival rate can be increased to about 8 months [22]. In our case, OS is 54 months and the patient continues systemic treatment.

(ADP-ribose) polymerase (PARP) inhibitors can have a hugely destructive effect on BRCA-mutated tumors. Patients who have germline or somatic mutations in BRCA are sensitive to PARP inhibitors [23]. The phase III POLO trial, presented at the 2019 ASCO Annual Meeting, showed that the PARP inhibitor olaparib significantly improved Progression-Free Survival (PFS) in patients with germline BRCA-mutated metastatic pancreatic cancer compared to a placebo when used as maintenance therapy. The median PFS was 7.4 months with olaparib versus 3.8 months with placebo (hazard ratio [HR], 0.53; 95% CI, 0.35-0.82; P= .004) [24]. In our case, PFS with Olaparib was 18 months.

In a final clinical trial result, no OS benefit for active maintenance treatment with Olaparib relative to a placebo in patients with metastatic PC and *BRCA* mutation was detected [25]. According to the authors, the POLO study was not powered enough to demonstrate a benefit of Olaparib on OS. Despite the lack of statistically significant OS administration of Olaparib provides a clinically meaningful benefit on many clinically relevant endpoints compared with placebo [25]. This clinical study is an excellent example of the need for further research to select the appropriate maintenance treatment and the best treatment options after PARP inhibitors.

A meta-analysis of published clinical trials total of 2,479 patients revealed that the incidence of PARPi-associated severe hematologic toxicities were, respectively: neutropenia: 32.9%; thrombocytopenia: 15.9%, and anemia: 9.1%. Olaparib was associated with an increased risk of severe neutropenia [26]. Our patient was diagnosed with 1st degree neutropenia and no other hematological toxicities during the treatment. Neutropenia was successfully treated with granulocyte colony-stimulating factors.

Considering the good performance status of the patient and the absence of concomitant diseases, surgical treatment of oligometastatic pancreatic cancer using a local surgical method was chosen. Recent studies indicate that patients may benefit from surgical treatment of oligometastatic disease based on personalized patient factors [27,28]. Although the efficacy of removing neuroendocrine and colorectal metastases has already been demonstrated, new randomized-controlled studies with specific inclusion criteria and primary endpoints are needed to establish higher standards in pancreatic cancer [29].

At the moment, our patient has disease progression and systemic treatment is the only available option. The main question is which systemic treatment regimen is the most suitable for our patient. As we have already discussed, the patient with the BRCA mutation has a good response to platinum-based chemotherapy, but our patient received it relatively recently (less than 6 months ago after the last course of platinum-based chemotherapy), so this treatment is not preferred at the moment. The phase III MPACT trial for metastatic PC showed improved Overall Survival (OS) and Progression-Free Survival (PFS) for first-line nab-paclitaxel (Abraxane) and gemcitabine (the AG combination). The median OS was 6.5 months (95% CI: 3.9–10.3) and the median PFS was 4.6 months (95% CI: 3–5.1) [30]. In phase 3, open-label, randomized NAPOLI-1 trial median PFS was 3.1 months in patients receiving liposomal irinotecan plus 5-fluorouracil and leucovorin (HR: 0.57; 95% CI: 0.43e0.76; P<0.0001) [31]. MEK inhibitors can be considered as a treatment possibility because a KRAS mutation was detected during genetic testing. A combination of MEK autophagy inhibitors may therefore be more beneficial [32]. For example, Trametinib plus hydroxychloroquine may

improve partial response [33]. However, this data is in the early preclinical and clinical stages, and only clinical trials are possible for patients.

Thinking about the future, it is important to mention that pathogenic variants in BRCA1 and BRCA2 are associated with a variable risk of gastrointestinal cancer, including colorectal, PDAC, as well as biliary and gastric cancers. Screening for pancreatic cancer is not established, although recent trials and international recommendations provide preliminary support for PDAC screening in high-risk individuals. The lack of accurate PDAC risk estimates leaves our patients and their families without a proper follow-up [34]. Potential benefits of pancreatic cancer screening include a suggestion of down staging compared to historical data, in that 75%-90% of screen-detected pancreatic cancers have been surgically respectable at diagnosis (which is markedly higher than historical rates of respectability with pancreatic cancers detected due to symptoms). There has also been a suggestion of improved mortality compared to historical data, with one study demonstrating an 85% 3-year OS rate after screen-detected pancreatic cancer in high-risk individuals. We should not forget to consider the potential for unnecessary interventions [35]. We believe that screening could help to develop better cancer care for our patients.

Conclusions

Pancreatic cancer with a BRCA mutation can be successfully treated based on genetic profiling and combined therapies. Personalized medicine is the key to successful pancreatic cancer treatment in the future. Further data is needed to better define the need for follow-up for patients with a high risk of BRCA2 mutated PDAC.

Abbreviations: PC: Pancreatic Cancer; WHO: World health Organization; PanNET: pancreatic Neuroendocrine Tumors; NET: Neuroendocrine Tumor; MRI: Magnetic Resonance Imaging; CT: Computerized Tomography; PET: Positron Emission Tomography; MTS: Metastasis; MDT: Multidisciplinary Team; ICU: Intensive Care Unit; NCI: National Cancer Institute of Lithuania; PDAC: Pancreatic Ductal Adenocarcinoma; OS: Overall Survival.

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