ID: 00965
Type: Poster
Topic: Miscellaneous

THE SPANISH FAMILIAL PANCRETIC CANCER REGISTRY: GENETIC ANALYSIS AND FOLLOW UP OF HIGH RISK INDIVIDUALS

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Introduction

Pancreatic cancer accounts for 2.3% of all types of cancers diagnosed and the incidence has continued to grow over the last 50 years. By 2020, it is estimated to become the second cause of cancer related death, just behind lung cancer. This type of tumor has not benefited from a personalized medicine approach and targeted therapies that are commonly used in other tumor types. Early diagnosis of pancreatic tumors is hindered due to the lack specific associated symptoms. 80% of cases present with non-resectable disseminated disease and only 15-20% are candidates for a potentially curative resection. However, 2 out 3 of these cases will recur or relapse within 3-6 months after surgery. Early detection is the key to improve the prognosis and quality of life of these patients. Thus, in 2009 the Spanish Pancreatic Cancer Registry was founded at the Ramón y Cajal Hospital with the aim to characterize families at high risk of developing pancreatic cancer.

Objectives

- Create a national-wide registry of high risk families
- To improve the understanding and the management of the disease via the molecular and genetic characterization of Familial Pancreatic Cancer.
- Offer a screening program for early cancer detection to at risk individuals within these families.
- Identify and validate novel minimally -invasive biomarkers for early detection.

Methodology

Cases with familial pancreatic cancer were identified in the Medical Oncology department of the Ramón y Cajal Hospital. Familial pancreatic cancer is defined as those who has at least two affected first-degree relatives. Families with a history of pancreatic cancer associated with other hereditary cancer syndromes, such as ovarian-breast, Lynch syndrome, Peutz-Jacobs syndrome, hereditary familial melanoma, chronic hereditary pancreatitis or pancreatic cancer at an early age are also included. A thorough family history is taken by the familial oncologist. The patient is explained the study and signs the informed consent with a team member. All participants answer an epidemiological questionnaire about toxic habits and other relevant diseases and blood samples are taken. Healthy, at risk individual are offered to participate in the screening program and are monitored annually via an MRI and EUS scan and an analysis of the tumor marker, CA19-9 in blood. Cases and high risk individuals are screened for a pathogenic mutations in 35 genes associated with familial cancer. Furthermore, somatic mutations were also assessed in circulating free DNA (cfDNA) via panel sequencing.

Results

10 national hospitals participating in the registry and at present there are 83 families registered with around 200 participants. Panel sequencing of 35 genes was performed in a total of 68 individuals included in the registry. This included 45 pancreatic cancer cases, 13 individuals diagnosed with other tumor types or pancreatitis and 10 high risk individuals participating in the early detection program.

Potentially pathogenic mutations were identified in 33 individuals, this included 20 pancreatic cancer patients, 2 patients with other cancer types/pancreatitis and 6 high risk healthy individuals. Potentially pathogenic mutations were found in DNA repair genes including BRCA2, MLH1, MSH2, FANCM and FANCC that are traditionally associated with other cancer syndromes, although their relevance in pancreatic cancer is starting to emerge. KRAS and p53 mutations were the most frequent somatic mutations found in cftDNA from sporadic cases by sequencing analysis, whereas BRAF, EGFR and KIT mutations were more frequently found in familial cases.

20 cystic lesions were identified in healthy high risk individuals via MRI, EUS or CT scans. 3 of these lesions were subsequently diagnosed as malignant lesions via FNA and histology. These 3 patients were less than 55 years of age and have subsequently undergone a successful surgical resection and are currently disease free with no signs or symptoms of the disease.

Conclusions

- Pathogenic mutations in genes typically associated with other cancer syndromes such as BRCA2, ATM, PALB2 (breast and ovarian cancer), MLH1 and MSH2 (Lynch syndrome) and FANCC and FANCM (Fanconi anemia) are also found in some familial pancreatic cancer cases.
- The identification of somatic potentially druggable mutations in cfDNA in familial cases may provide a strategy for personalized medicine in this sub group of cases.
- The screening program is effective for the early detection of pancreatic cancer and ideally this would be available at the national wide level to all high risk families.

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