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Precision Oncology in Pancreatic Cancer. From Surgery- to Genetic-Based Chemotherapy

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INTRODUCTION

Pancreatic ductal adenocarcinoma is one of the most lethal forms of solid tumors. These tumors arise from the exocrine component of the pancreas, probably from acinar stem cells[1-3], and are characterized by an unusual amount of stroma, which includes a heterogenic assortment of cells, such as fibroblasts and immune and endothelial cells. The most important risk factors for this neoplasia are smoking and a family history of pancreatic tumors, but chronic pancreatitis, diabetes mellitus, obesity, and several new factors now being studied are also important[4]. Recently, Aykut *et al.* have shown that the commensal microorganisms that colonize the epithelial surfaces of the human body (known as microbiota) produce small molecules with both local and systemic effects on cancer onset, progression, and therapy response[5]. Pancreatic ductal adenocarcinoma presents a 1000-fold increase in intratumoral bacteria and a 3000-fold increase in diverse fungi[6,7], which are thought to be key in tumoral progression and therapeutic response. These results open the path for novel diagnostic, prognostic, and treatment strategies[8,9]. Patients with this disease have a 5-year survival rate of <5%, and pancreatic and liver cancers are predicted to surpass breast, prostate, and colorectal cancers to become the second- and third-leading causes of death in the United States by 2030[8-10]. Even more worrisome, an upward incidence and mortality trend are predicted to position Latin America as the second world region by 2040, only after Africa[10]. Surgery is still the mainstay of treatment. Despite the improvement in surgical morbidity and mortality, the impact on overall survival is limited, with only 5% of patients surviving more than 5 years.

PERSPECTIVE

Treatment of pancreatic carcinoma is determined by clinical staging based on the current National Comprehensive Cancer Network guidelines. The most advanced stage patients present predominantly metastatic systemic disease (commonly involving liver metastasis), in which surgical treatment is futile, and chemotherapy is the first line of treatment. The local advanced stage is defined as an absence of systemic disease, but when there is the involvement of the superior mesenteric artery or celiac artery or invasion

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of the portomesenteric vein, it is not amenable to reconstruction. At this stage, chemotherapy may help to downstage the neoplasm to make it borderline resectable and allow surgical resection. The resectable stage is defined by the absence of systemic disease and arterial involvement; contact of the portomesenteric vein may exist involving <180° of its circumference making it technically possible to perform a viable reconstruction. Surgical resection is still the mainstay of treatment at the resectable stage[11].

There is currently a shift toward neoadjuvant chemotherapy for these tumors. A patient-based meta-analysis of 355 cases of local, advanced pancreatic cancer in patients who underwent neoadjuvant FOLFIRINOX-based chemotherapy, showed an overall survival time of 24 months. Interestingly, in this cohort of patients, only 25% of patients underwent surgery, so the survival advantage was achieved in 75% of cases with chemotherapy alone; this speaks to the important advantage of modern chemotherapy in the survival of pancreatic cancer patients[12]. Despite the evident advantages of chemotherapy in the locally advanced setting for downstaging and as adjuvant therapy with FOLFIRINOX-based regimens, no evidence exists of its benefit for resectable or borderline-resectable cases. A recent Phase III trial with gemcitabine-based neoadjuvant chemoradiation failed to demonstrate differences in overall survival rates[13].

Recent international efforts have characterized the genomic landscape of pancreatic tumors[14]. The studies have shown that a significant fraction of these patients presents predictive germline and somatic biomarkers that could help with diagnosis and prognosis[15]. Besides the well-known mutations in *KRAS, TP53, CDKN2A,* and *SMAD4,* a long list of less frequent mutations has been discovered, including chromatin-regulating genes such as *MLL, MLL2, MLL3,* and *ARID1A*; axon-guidance genes such as *ROBO1*, 2, and 3; DNA-damage genes such as *ATM*; and other novel genes such as *KDM6A, PREX2,* and *RNF43*[16]. Following the established path for breast tumors, a limited number of molecular pancreatic subtypes have been described, based on their transcriptome (squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine-exocrine tumors)[16] or on their chromosomal structural variant (stable, locally rearranged, scattered, and unstable)[17]. These subtypes present differences in clinical outcomes and therapeutic response. For example, the Pancreatic Cancer Action Network recently showed that 50% of the tumors presented actionable genomic findings (e.g., alterations that can be used for guiding targeted therapy)[18]. In this study, patients showed a superior and progression-free survival rate when their treatment was guided by the genomic results, although to a small degree (4.1 months vs. 1.9 months). Another study[19] demonstrated that 48% of patients with pancreatic adenocarcinoma presented actionable mutations, with 30% of them undergoing a change in their management following these results. Notwithstanding the multiple genomic alterations found in these studies, the most common actionable mutations affected the DNA damage pathway, particularly the homologous recombination (HR) process. Mutations in genes related to this pathway are present in nearly 10%[20] of tumors, and an additional 7-7.6% have an HR deficiency without evidence of mutations[19]. Several preliminary studies show that HR deficiency predicts a patient's response to cisplatin- or oxaliplatin-based chemotherapy, which is the basis for ongoing studies using polyadenosine diphosphate-ribose polymerase (PARP) inhibitors in these patients. Although these studies are encouraging, the required replication and clinical translational trials needed to establish the role of genomic precision strategies for cancer management are still scarce.

One of the least explored interventions in pancreatic cancer prevention is identifying people at high risk for the disease. Because most of the known, modifiable risk factors are relatively common (smoking, diabetes mellitus, and obesity), pinpointing specific groups for pancreatic-directed interventions are rather difficult. Nevertheless, contrary to the majority of tumors, pancreatic cancer patients present a higher prevalence of genetic predisposition genes. Diverse studies have proposed that between 10% and 20% of pancreatic cancer patients have an associated genetic predisposition component, including familial pancreatic cancer; diverse inherited tumor syndromes, such as Peutz–Jeghers and Li–Fraumeni syndrome; and single germline pathogenic mutations (Table 1). This high prevalence offers opportunities to provide secondary prevention, give affected families genetic counseling, and explore novel therapeutic approaches in these patients. However, these reports are based mainly on the populations of the US and the EU and lack diversity. Because the prevalence of

Table 1. Genetic risk factors, genes, relative risk, and associated tumors for pancreatic cancer

Risk factor	Genes	Risk	Associated tumors
Peutz-Jaeger syndrome	*STK11/LLDI*	132	Esophageal, stomach, small intestine, utrine, ovarian, etc.
Hereditary pancreatitis	*Trypsinogen/SPINK-1*	53	
FAMMM	*P16/CDKN2A/MTS1*	38	Melanoma
FAP	*APC*	4	Colon, duodenum, thyroid, brain, ampulla, etc.
Lynch, HNPCC	*MSH1/2, PMS1/2, MSH6, EPCAM*	4	Colorectal, endometrial, ovarian, stomach, small intestine, etc.
HBOC	*BRCA1/2, PALB2*	2-3	Breast, ovarian, and prostate
Li-Fraumeni	*TP53*	?	Sarcomas, breast, brain, adrenal glands
Ataxia telangectasia	*ATM*	?	Leukemia, lymphoma
Cystic fibrosis	*CFTR*	?	
Other?	*TET2, DNMT3A, POLN, POLQ, ASXL1, FANCG, FANCC, FANCM, RAD54L, ESCO2, BUB1B*	?	?

FAMMM: familial atypical malignant mole and melanoma; FAP: familial adenomatous polyposis; HNPCC: hereditary non-polyposis colorectal cancer; HBOC: hereditary breast and ovarian cancer.

genomic variants differs between populations and the penetrance of the phenotypic consequence of these variants depends not only on genomic epistasis but also on environmental factors, it is urgent to determine the prevalence of pathogenic germinal variants in underrepresented cohorts, including Mexican patients, to propose a directed and low-cost genomic diagnostic test. Several authors have recently underscored population differences in pancreatic cancer (for example, Geographic and Ethnic Heterogeneity of Germline *BRCA1* or *BRCA2*). Recent reports have shown that even relatively small gene panels can detect a genetic predisposition for at least 10% of patients[21]. These findings prompted the American Society for Clinical Oncology to convey a provisional clinical opinion recommending that all patients with pancreatic cancer undergo risk assessment for genetic predisposition for these tumors[22]. The reason behind this recommendation is the striking 42% of patients with no family history of pancreatic cancer who would not have met the current recommendations for screening[23].

In addition, determining the germinal genetic alterations that predispose one to pancreatic cancer could also have important therapeutic implications. Both sporadic and genetically predisposed pancreatic tumors can be deficient in homologous recombination, mismatch repair, and STK11 genes. These tumors, and particularly those presented by patients demonstrating genetic susceptibility, could be sensitive to PARP inhibitors/platinum combinations, immune checkpoints, and mTOR inhibitors. Indeed, as of February 2020, there are 42 Phase II and 6 Phase III active clinical trials involving targeted therapy for pancreatic cancer in the USA, which show the general interest in developing a model for precision therapy to improve outcomes among pancreatic cancer patients. For example, a recent veliparib trial showed that with cisplatin/gemcitabine alone, 80% of patients with BRCA mutations presented a measurable response. This tailors chemotherapy to a less toxic regimen than FOLFIRINOX, based on BRCA mutation status[24].

Using a directed gene panel designed for our population in a selected group (patients with at least one first- or second-degree relative with previous pancreatic, breast, or predisposition syndrome-associated tumors) could be not only clinically relevant but also cost-effective. Alternatively, a risk model such as the Bayesian PancPRO[25] could be developed and validated in our country, although this would need an important investment in genome-wide studies.

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