

HIGHLIGHT ARTICLE

Pancreatic Cancer: Updates on Translational Research and Future Applications

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Summary

Pancreatic cancer is one of the most lethal malignancies with a mortality rate almost equal to its incidence. It is ranked as the fourth leading cause of cancer-related deaths in the United States, and despite intensive basic and clinical research over the last few years, the survival benefit for the majority of patients with pancreatic cancer is still disappointing. Due to the absence of specific symptoms and the lack of early detection tests, pancreatic cancer is usually diagnosed at an advanced inoperable stage and palliative chemotherapy with the purine analogue gemcitabine in combination with the targeted agent erlotinib, remains the mainstay method in the management of these patients. Therefore, there is an imperative need for new findings in the translational research field with prognostic, predictive and therapeutic value. In this paper we summarize five most interesting research abstracts as presented at the 2013 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. In particular, we focus on Abstract #141 which investigates the interaction between liver and pancreatic organ damage in patients with pancreatic cancer and the potential contribution of the patatin-like phospholipase domain containing 3 (PNPLA3) gene variation in pancreatic cancer development and on Abstract #149, in which, the prognostic and predictive role of SWI/SNF complex, a chromatin-remodeling complex, is examined. The key role of pharmacogenomics, in terms of predicting response and resistance to chemotherapy in pancreatic cancer patients, is analyzed in Abstract #142 and the contribution of circulating tumor cell detection in the early diagnosis of pancreatic cancer, allowing the avoidance of more invasive procedures like EUS-FNA, is discussed in Abstract #157. Lastly, in Abstract #164, the diagnostic utility of YKL-40 and IL-6 in pancreatic cancer patients is investigated.

What We Knew Before the 2013 ASCO Gastrointestinal Cancers Symposium?

Pancreatic cancer is an aggressive malignancy with a dismal survival rate. Even though remarkable progress has been achieved in the field of translational research, it has not yet resulted in equal advances in every day clinical practice and a lack of clinically significant improvements in prognosis and treatment of the disease is still observed. Several risk factors related to pancreatic cancer have been previously explored and identified. Such risk factors include cigarette smoking [1], obesity [2], diabetes mellitus [3], metabolic syndrome [4], increased alcohol consumption [5], chronic pancreatitis [6] and genetics [7]. Recent studies have also associated hepatitis B viral (HBV) infection

with increased risk of pancreatic cancer [8, 9]. Many of these factors also account for primary liver cancer, justifying the close interaction between these two organs in terms of organ damage and cancer development.

It is commonly observed that most pancreatic cancer patients are diagnosed at advanced stage with inoperable locally advanced tumors or metastatic disease, mainly because of non-specific symptoms and a lack of tests that will allow early diagnosis. Currently, the diagnostic strategies used, include radiological techniques, endoscopy, laboratory tests such as the serum marker CA 19-9 and invasive techniques that will allow cytological or histological proof of cancer. Thus, new diagnostic tools with high sensitivity and specificity that will achieve early diagnosis of the disease are urgently needed.

At the moment, literature provides strong evidence of efficacy only for a limited number of chemotherapy drugs such as gemcitabine, platinum agents and capecitabine, one targeted agent (erlotinib) and possibly for radiotherapy in the locally advanced disease [10]. The field of pharmacogenomics in pancreatic cancer is rapidly evolving, aiming at a more individualized patients care; therefore, several genetic

Keywords Adenocarcinoma; Biological Markers; Pancreatic Neoplasms; Pharmacogenomics; Translational Medical Research
Abbreviations NAFLD: nonalcoholic fatty liver disease; PNPLA3: patatin-like phospholipase domain containing 3
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loci have been identified to predict toxicity (e.g., RRM1, CDA, DPYD, UGT1A1) or efficacy (e.g., HuR, DCK, TS, ERCC1) of the reported drugs commonly used in the treatment of pancreatic cancer, even though they have not reached yet the clinical stage [11]. Gene mutations and polymorphisms of the oncogenes *K-ras*, *HER-2/neu*, *p16INK4a*, *notch1*, *Akt-2* and *COX-2* and of the tumor suppressor genes *p53*, *DPC4*, *FHIT* and *BRCA2* are the most frequently observed in pancreatic cancer [11]. Further research in the fields of translational science and pharmacogenomics will hopefully lead to the identification of prognostic and predictive biomarkers with potential applications in clinical practice.

What We Learnt at the 2013 ASCO Gastro-intestinal Cancers Symposium?

Pancreatic Injury, Genetic Variation of PNPLA3, and Risk of Pancreatic Cancer. (Abstract #141 [12])

As aforementioned, obesity, diabetes mellitus, metabolic syndrome and hepatitis B viral (HBV) infection are common risk factors accounting for both liver and pancreatic cancer development, certifying the potential interaction between these two organs in the ground of organ damage and cancer development. Several factors have been strongly associated with nonalcoholic fatty liver disease (NAFLD) development and patatin-like phospholipase domain containing 3 (PNPLA3) gene has been identified for significantly involving in the genetic susceptibility of NAFLD in humans. A single nucleotide polymorphism in PNPLA3 gene (rs738409 C/G) has been associated with NAFLD and disease severity [13]. Moreover, the genetic variant rs738409 C/G in the PNPLA3 gene has been reported to increase the risk of cirrhosis in various liver diseases, and is a strong predictor of hepatocellular carcinoma occurrence among patients with cirrhosis [14].

Mohammed Aly *et al.* conducted a study in MD Anderson Cancer Center with 544 pancreatic cancer patients and 498 healthy individuals that served as controls, aiming at investigating the synergism between pancreatic and liver organ damage in pancreatic cancer patients and the influence of the rs738409 C/G polymorphism on pancreatic cancer development. The researchers reported that 102/544 pancreatic cancer patients (18.8%) in their study presented evidence of pancreatic injury, including tissue damage, chronic inflammation and fibrotic events, whereas in 79/544 pancreatic cancer patients (14.5%), NAFLD was observed and particularly in patients with chronic pancreatic inflammation (pancreatitis). Furthermore, a

statistically significant coappearance of both pancreatitis and liver cirrhosis was observed in medically obese pancreatic cancer patients, but not in patients without a history of obesity, which strengthens the role of obesity in the pathogenesis of both clinical conditions. No statistically significant correlation between PNPLA3 gene variation and pancreatic cancer occurrence was reported. Thus, researchers concluded that between these two organs, differences might exist as to the genetic susceptibility of NAFLD and its influence on cancer occurrence.

The Clinical Significance of SWI/SNF Complex in Pancreatic Cancer. (Abstract #149 [15])

The SWI/SNF complex is a chromatin-remodeling complex with a significant role in remodeling nucleosomes and modulating transcription, participating thus in the regulation of gene expression. It consists of a catalytic subunit that may be either BRG1 or BRM and various associated proteins, known as BAF, able to recruit the complex to specific promoters and regulate its activity. Strong evidence exists to support that this complex has a significant role in tumor suppression, as inactivating mutations in several SWI/SNF subunits have been identified in a variety of cancers such as lung, prostate, breast, colon and pancreas [16].

Masakatsu Numata *et al.* studied 68 patients with pancreatic cancer who underwent tumor resection, aiming to correlate the levels of SWI/SNF subunits expression in cancer tissue with disease prognosis. Immunostaining techniques were performed in cancer tissues against the following antigens: BRM, BRG1, BAF250a, BAF180, and BAF47, all components of the SWI/SNF complex, and the expression levels were characterized as “low” or “high”. Statistical analysis showed that the expression levels of BRM were related to tumor size, T factor, metastasis, lymphatic invasion and cancer stage and the expression levels of BRG1 were related to histology and cancer stage. Lastly, the expression levels of BAF180 and BAF47 were related to tumor size and lymphatic invasion respectively (Table 1). Moreover, high expression levels of BRM and low expression levels of BAF180 were independently associated with worse prognosis and limited survival in pancreatic cancer patients. In patients that received gemcitabine as adjuvant chemotherapy, high-BRM and low-BAF180 expression levels were also associated with poor prognosis and dismal overall survival. Based on the data presented, authors suggested that high-BRM and low-BAF180 expression levels could be used as prognostic biomarkers in pancreatic cancer.

Table 1. Factors related to the expression levels of the SWI/SNF components (Abstract #149 [15]).

	Tumor size	T Factor	M Factor	Lymphatic invasion	Stage	Histology
BRM	+	+	+	+	+	
BRG1					+	+
BAF180	+					
BAF47				+		

Use of Pharmacogenomic Modeling in Pancreatic Cancer for Prediction Of Chemotherapy Response and Resistance. (Abstract #142 [17])

Vineet Sangar *et al.* presented the preliminary results of a study in 46 patients with inoperable pancreatic adenocarcinoma. In these patients, tumor progenitor cells were isolated from peripheral blood before patients received any cytotoxic treatment and at disease progression. Chemosensitivity and gene expression profiling was performed, aiming to predict efficacy and resistance to cytotoxics. From the 46 patients recruited, 35 patients presented with disease response and 11 patients had disease progression after first line treatment. Published data suggest that patients treated with cytotoxics, who were predicted to be effective, had a significantly better clinicopathological outcome against patients predicted to be ineffective. In the 11 patients presenting disease progression, evidence of chemoresistance was observed when tumor progenitor cells extraction and analysis was repeated at disease progression. Furthermore, overexpression of Hedgehog pathway was associated with resistance to gemcitabine and response to 5-FU based therapy, and pathway analysis suggested that ErbB3, ARE/Nrf2 and insulin pathways were associated with chemoresistance. Authors concluded that tumor progenitor cells isolation and gene expression profiling might be a useful predictive biomarker in patients with inoperable pancreatic adenocarcinoma.

Usefulness of Circulating Tumor Cell Detection in Pancreatic Adenocarcinoma Diagnosis. (Abstract #157 [18])

In patients with inoperable pancreatic tumors, EUS-FNA and cytological examination are considered to be the first diagnostic procedures according to international guidelines. Paul Basile *et al.* proposed an alternative solution for early diagnosis in patients with pancreatic tumors based on circulating tumor cell detection in peripheral blood. From January 2011 until March 2012, 40 patients were studied in an attempt to evaluate the accuracy of this diagnostic method. All patients presented with solid pancreatic tumors, and before EUS-FNA was conducted, a sample of peripheral blood was collected and CTCs were detected. Morphological criteria were used to determine cell malignant transformation:

- nuclear diameter greater than 14 μ ;
- anisocytosis;
- anisocaryosis;
- irregularities in nuclear membrane;
- large nucleolus;
- clots of tumoral cells with platelets and fibrin.

In 27/40 patients (67.5%) the diagnosis of pancreatic adenocarcinoma was based on either cytological-histological confirmation with the use of FNA (21/40 patients, 52.5%) or surgical biopsy, or based on metastatic disease confirmation and increased serum levels of CA 19.9 (more than 10-fold the upper

reference value). In 15 patients circulating tumor cell detection in peripheral blood was positive. The sensitivity and specificity of this method were 55.5% and 100%, respectively compared to 77.8% and 100% for the EUS-FNA procedure. The diagnostic accuracy was 70% for the circulating tumor cell detection and 85% for the EUS-FNA. Researchers suggested that circulating tumor cell detection could play a significant role in the early diagnosis of pancreatic cancer; therefore, it should be introduced as first-line diagnostic procedure, leading even to the avoidance of more invasive procedures like EUS-FNA.

Pretreatment Plasma Concentrations of YKL-40 and IL-6 in Patients with Pancreatic Cancer: Potential Diagnostic and Prognostic Biomarkers. (Abstract #164 [19])

Nicolai Schultz *et al.* conducted a prospective study with 556 pancreatic cancer patients in an attempt to investigate the role of YKL-40 and IL-6 in the diagnosis and prognosis of pancreatic cancer patients. In all 556 patients, pretreatment plasma concentrations of YKL-40 and IL-6 were determined by ELISA. One-hundred and fifty-two out of 556 patients (27.3%) underwent a surgery and were treated with adjuvant gemcitabine, whereas 404/556 patients (72.7%) had inoperable locally advanced tumors or metastatic disease and were treated with palliative chemotherapy. Data presented suggest that all 3 biomarkers (YKL-40, IL-6, CA 19.9) were predictive of pancreatic cancer and had a tendency to increase with more advanced stage. In patients that underwent surgery, only pretreatment levels of IL-6 and CA 19.9 were associated with poor overall survival, in contrast with unresectable patients in whom all 3 biomarkers were independently associated with dismal overall survival. Authors concluded that pretreatment plasma concentrations of YKL-40 and IL-6 may serve as useful diagnostic and prognostic biomarkers in pancreatic cancer patients.

Discussion

Over the last few years enormous progress has been achieved in the fields of translational research and pharmacogenomics. However, this progress often does not translate to clinically meaningful results; therefore, the prognosis and overall survival in patients with pancreatic cancer remain poor. The studies previously presented demonstrate the trend of pancreatic cancer research to move forward and expand its applications in every day clinical practice.

In almost 1/5 patients with pancreatic cancer, evidence of pancreatic injury coexist, along with fatty liver disease (NAFLD) and chronic pancreatic inflammation. In medically obese pancreatic cancer patients, a significant coappearance of both pancreatitis and liver cirrhosis was observed, which strengthens the role of obesity in the pathogenesis of both clinical conditions, and even though pancreas and liver are organs with many similarities in terms of organ

damage and cancer development, differences in the genetic susceptibility of NAFLD and its influence on cancer occurrence were observed. Thus, nonalcoholic fatty pancreatic disease (NAFPD) in pancreatic cancer patients seems as a promising ground for future research.

In the field of translational research, new findings were also reported. High expression levels of BRM and low expression levels of BAF180 (subunits of the SWI/SNF complex) were independently associated with poor prognosis and dismal overall survival in pancreatic cancer patients, but also in patients receiving gemcitabine as adjuvant chemotherapy, serving thus as potential prognostic biomarkers. Similarly, pretreatment plasma concentrations of YKL-40 and IL-6 were predictive of pancreatic cancer and were independently associated with worse overall survival in patients with inoperable pancreatic cancer, indicating the potential utility of YKL-40 and IL-6 as diagnostic and prognostic biomarkers. Lastly, circulating tumor cell detection in peripheral blood might be a useful minimally-invasive diagnostic tool in pancreatic cancer patients, able to achieve early diagnosis with acceptable sensitivity and specificity, and even allow the avoidance of more invasive procedures like EUS-FNA.

In the field of pharmacogenomics, extensive research efforts aim at the development of new applications with prognostic, predictive and therapeutic value that will allow physicians to choose the safest and most effective management for their patients, with a view to molecular guidance for clinical diagnosis and personalized patients care. In that direction, Vineet Sangar *et al.* reported that tumor progenitor cells isolation and gene expression profiling might serve as a useful predictive biomarker in patients with unresectable pancreatic adenocarcinoma. All findings presented above are quite promising, but not enough in order to be applied in the clinical setting. More clinical trials along with the identification of more biomarkers with prognostic and predictive value are required in order to produce more definite results for this lethal disease.

Conflicts of interest The authors have no conflicts to disclose

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