

HIGHLIGHT ARTICLE

Translational Research. New Findings and Potential Future Applications in Pancreatic Adenocarcinoma

Highlights from the "2012 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 19-21, 2012

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Summary

The current achievements in pancreatic cancer diagnosis and treatment are disappointing for patients and clinicians alike. Still, in the dawn of 2012, most patients are diagnosed at a late stage where cure is not feasible, with the majority going to succumb within the same year of diagnosis. Thus, the only hope for early and diagnosis and radical treatment is the invention of diagnostic and prognostic tests which might predict accurately patients who may develop this disease and those who have the most aggressive potential, so clinician adopt the appropriate strategy. In this paper we summarize the findings from the three most interesting research abstract as presented at the 2012 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. In particular, we focus on Abstract #160 which shows the diagnostic utility of microRNA serum profiling in pancreatic cancer patients, on Abstract #201 which suggests a potential prognostic role of transforming growth factor (TGF)-beta pathway in advanced pancreatic cancer, and on Abstract #165 which shows that protein S100A4 might be a new, potentially useful, predictive biomarker of gemcitabine efficacy.

What Did We Know Before 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium?

So far, there are no specific guidelines on pancreatic cancer screening and diagnosis despite extensive research that has been undertaken over the last years [1]. Diagnosis is based on cytological or histological proof of cancer in a relevant clinical scenario. Following diagnosis and a multidisciplinary discussion, patients are either directed to surgical treatment or offered a systemic therapy with the addition sometimes of radiation. There are often difficulties in correct diagnosis despite extensive investigations. Even after a correct and rapid diagnosis and in spite of a satisfactory operation or adequate adjuvant treatment, we often feel the disappointment from early relapses. Thus, there is an urge for tests with high diagnostic ability, both sensitive and specific, and for biomarkers of response or of prognosis of this disease.

Keywords Adenocarcinoma; Biological Markers; gemcitabine; Pancreatic Neoplasms

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What Did We Learnt from 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium?

In this review, we summarize the most notable scientific data on pancreatic cancer diagnosis and prediction of treatment efficacy, hoping that may contribute at some point in the real clinical setting where patients are managed.

Diagnostic MicroRNA Serum Profile in Pancreatic Cancer (Abstract #160 [2])

MicroRNAs (miRNAs) are short ribonucleic acid (RNA) molecules that play role in gene regulation and in regulation of various cellular functions. It has been shown that miRNAs play also role in oncogenesis, apoptosis and angiogenesis (Figure 1) [3]. A team of researchers from Denmark, extracted, purified and stored RNA from the serum of 139 patients diagnosed with pancreatic cancer, 17 patients with chronic pancreatitis and 50 healthy individuals that served as controls [2]. They aimed to identify specific miRNAs that may distinguish pancreatic cancer patients from those with chronic pancreatitis or not disease at all. They measured miRNA expression by array human microRNA A and B cards (TaqMan[®] v3.0, Applied Biosystems, Foster City, CA, USA) and profiled 768 miRNAs. By using a logistic regression analysis, they

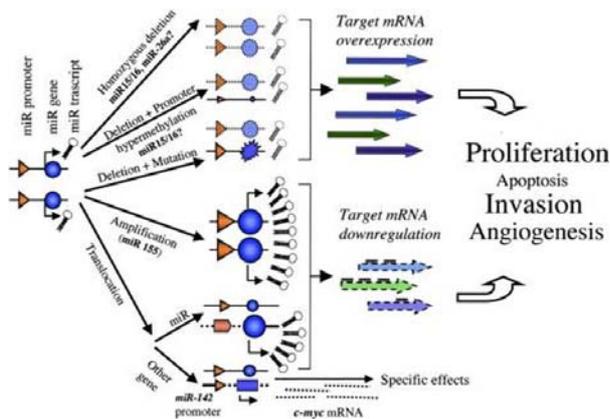


Figure 1. The role and mechanisms of function of miRNAs (adapted from Calin *et al.* [3]).

identified several miRNAs related to pancreatic cancer, and those with $P < 0.000001$ were subsequently evaluated in a multivariate analysis. All 206 patients had satisfactory miRNAs on their serum samples. After excluding the miRNAs considered as undetermined, 85 miRNAs were tested in the univariate analysis. Of those, 12 were then evaluated in a multivariate analysis and 7 were found finally associated with pancreatic cancer (6 with statistical significance). Decreased expression of these seven miRNAs in the diagnostic panel was associated with pancreatic cancer. The authors did not disclose the names of these potential diagnostic miRNAs.

Transforming Growth Factor (TGF) Beta Pathway and Clinical Outcome of Pancreatic Cancer (Abstract #201 [4])

Transforming growth factor (TGF) beta is a family of proteins that, through their actions on membrane serine/threonine kinase receptors (TGF-beta-R1/ R2), regulate downstream molecules (smad transcription regulators) and act either as tumor suppressors in the early stage of tumorigenesis or tumor promoters at the later stage of the disease [5]. Javle *et al* from M.D Anderson Cancer Center, Huston, TX, USA, investigated the prognostic role of TGF-beta signaling pathway in pancreatic cancer [4]. The authors measured the plasma levels of TGF-beta-1 in 643 pancreatic cancer patients by using the multi-array human TGF-beta-1 assay (Meso Scale Discovery, Gaithersburg, MD, USA) and tested for three single nucleotide polymorphisms of *TGFBI* gene by the TaqMan® (v3.0, Applied Biosystems, Town, Country) assay. They also measured the expression of TGF-beta-R2 and smad4 protein by immunohistochemistry (score 0-3) in 86 biopsies. Association of the TGF-beta levels and the expression of TGF-beta-R2 and smad4 protein immunohistochemistry score with overall survival was performed by Kaplan Meier and log-rank tests as well as multivariate analysis taking into account other clinical parameters (performance status, age, initial stage, and CA 19-9 levels). The authors reported a

significant association of plasma TGF-beta-1 with overall survival in the 355 patients with locally advanced and metastatic disease. Patients with low levels of TGF-beta-1 showed better survival than those with levels higher than 19.05 ng/mL (40 *versus* 27.7 weeks; log-rank $P=0.0125$). On the contrary, there was no significant association of survival with plasma TGF-beta-1 levels in the 288 surgical patients' cohort. Other interesting findings were the association of complete loss of smad4 expression (score 0 by immunohistochemistry) with significantly worse survival (hazard ratio: 1.85; 95% CI: 1.06-3.23; $P=0.03$) and a trend to resistance to gemcitabine-based treatment (46.5% *versus* 38.1% tumor progression; $P=0.069$) as compared to high smad4 expression. As far as the genotypic testing is concerned, it was found that the single nucleotide polymorphism *TGFBI* -1346T>C CT/TT genotype was associated with worse overall survival (hazard ratio: 1.21; 95% CI: 1.02-1.45, $P=0.03$). These findings may prove helpful in treatment decisions and the management of patients identifying those with worse prognosis and less likely to respond to gemcitabine chemotherapy.

S100A4 as a Biomarker of Resistance to Gemcitabine: A Secondary Analysis of RTOG 9704 (Abstract#165 [6])

Protein S100A4 belongs to the S100 family of EF hand calcium-binding proteins which are located intracellularly and have various roles such as the cell cycle progression and differentiation, cellular motility, invasion, and tubulin polymerization. Driven by preclinical data which suggested that S100A4 induces gemcitabine resistance [7], Tempero *et al* tested the potential role of S100A4 protein expression as a predictive biomarker of gemcitabine resistance on patients treated with gemcitabine or infusion 5-fluorouracil (5-FU), in the Radiation Therapy Oncology Group (RTOG) 9704 adjuvant randomized trial [6]. Retrospective evaluation of S100A4 expression by ICH on 184 patients treated in this study was performed. Disease specific survival and correlation with S100A4 expression was estimated on univariate (Kaplan-Meier method) and multivariate (Cox proportional hazards model) analysis. In this study, 97 patients had received 5-FU and 87 gemcitabine chemotherapy. In patients with negative S100A4 expression, the disease specific survival was better in the gemcitabine arm with hazard ratio 1.85, (95% CI: 0.96-3.56; $P=0.066$) whereas in the 5-FU arm hazard ratio was 0.93 (95% CI: 0.53-1.63; $P=0.80$). The 2-year disease specific survival for S100A4-negative or positive patients on the gemcitabine arm were 59% and 37%, in contrast to the 5-FU arm which were 26% and 39% respectively. The authors concluded that though not statistically significant, S100A4 overexpression is predictive for resistance to gemcitabine and validation of the results in a larger prospective study is warranted.

Discussion

We need to acknowledge that the speed of technological advances is enormous. This often does not translate to clinically meaningful results, as clinicians often hardly understood their impact, exact applications and their technical limitations or disadvantages. This reality necessitates the cooperation of physicians with bioinformatics specialists and other professionals in order to get the best from the finest available facilities.

The field of microarrays, bioengineering and genetic interference is very promising. In fact, when more experience is gained and elegant handling of their potentials is achieved, we expect to see great novel achievements.

For the time being, we do not have enough data to apply the genetic information (miRNAs) presented above in the clinical setting. Similarly, the data regarding the role of TGF-beta are not robust to change practice. On the other hand, though the results regarding the predictive role of S100A4 in gemcitabine based chemotherapy were not statistically significant, they need testing in a large prospective trial, and if confirmatory they may provide a useful tool in patients' selection at the era of personalized medicine.

Conflict of interest The authors have no potential conflicts of interest

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