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HIGHLIGHT ARTICLE

Identification of Prognostic and Predictive Markers in Pancreatic Adenocarcinoma

Highlights from the "2011 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 20-22, 2011

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Summary

Pancreatic cancer remains a significant cause of morbidity and mortality. While increasing treatment options have improved outcomes for many patients, they have also complicated decision-making for treatment. Unfortunately, most patients with pancreatic cancer die from their disease. Prognostic and predictive markers could play a role to improve treatment by identifying patients who may or may not require a given therapy, and determining those most likely to benefit from a therapy. At the 2011 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium held in San Francisco, January 2011, several interesting abstracts were presented that focused on prognostic and predictive markers associated with pancreatic adenocarcinomas. These abstracts discuss progress made in identifying molecular subtypes of pancreatic cancers that may provide insight into selection of patients likely to benefit from certain therapies.

What Did We Know Before 2011 ASCO GI Cancer Symposium?

Pancreatic cancer constitutes 6% of all cancers in the USA, and is the fifth most common cancer. The incidence of pancreatic adenocarcinoma is approximately 12 per 100,000 in the USA, which is slightly increased since 1975, and the lifetime risk is 1 in 71, with median age of diagnosis at 72 years. Recently, the prevalence of pancreatic cancer has increased by 52% over the last decade, as a reflection of the population at risk increase by aging “baby boomers”.

The prognosis of patients with pancreatic cancer remains poor. Patients frequently present with distant metastases, which are often occult at the time of diagnosis and the 5-year survival rate is 5.6% for all patients diagnosed with pancreatic adenocarcinoma. Treatment for patients with potentially curable disease remains challenging, and the 5-year survival for patients with early stage disease is estimated at 15%, with median survival for patients with locally advanced disease remains limited at 6 to 11 months [1]. The main challenges in the treatment of pancreatic adenocarcinoma include understanding tumor behavior and identification of predictive biomarkers for treatment success that may provide insight into selection of patient subsets that may benefit from certain therapies.

Key words Adenocarcinoma; Biological Markers; MicroRNAs; Molecular Epidemiology; Nomograms; Pancreatic Neoplasms

Abbreviations LASSO: least absolute shrinkage and selection operator

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What We Learned at 2011 ASCO GI Cancer Symposium

Hereditary Pancreatic Cancer, Familial Pancreatic Cancer and Syndromes Associated with Pancreatic Cancer

As surgery plays a central role in potentially curable patients with pancreatic adenocarcinoma, identification of more patients with early stage disease amenable to resection may have a substantial impact on survival. Identification of patients at risk for development of pancreatic cancer may provide an opportunity for aggressive screening and earlier detection of cancer in this subset of patients. Dr. Gloria Petersen from the Mayo Clinic presented data surrounding hereditary pancreatic cancer, epidemiology, genetic testing and clinical applications. In addition to age, other risk factors for the development of pancreatic cancer have been identified, including family history, smoking, race, obesity, diabetes, chronic pancreatitis, and certain dietary factors. The Mayo group is investigating the

relationship between new late onset type 2 diabetes and pancreatic cancer and has found an observed:expected ratio of pancreatic cancer of 7.94, with 1 in 125 new onset diabetes cases diagnosed with pancreatic cancer within 3 years [2].

Approximately 10% of patients with pancreatic adenocarcinoma have a first-degree relative with pancreatic cancer. The risk of developing pancreatic cancer for an individual with at least one first-degree relative is 2 to 3 fold increased [3, 4, 5, 6]. Recently, an increase in prevalence of familial clusters has been identified and study of family aggregations demonstrates an association with known hereditary syndromes in approximately 3% of cases. Study of family clusters has also identified cancer gene mutations.

Syndromes and genes that have been associated with pancreatic cancer include hereditary pancreatitis (RR 50; PRSS1-cationic trypsinogen), hereditary colorectal cancer (RR 2-5; APC, MSH2, MLH1), hereditary breast/ovarian cancer (RR 5-10; BRCA2) familial atypical multiple mole melanoma (RR 15-65; CDKN2A-p16) [7], Peutz-Jeghers syndrome (RR 130; STK11/LKB1), Fanconi's anemia (FANCC), [8] and cystic fibrosis (CFTR) [9, 10].

Patients with Fanconi's anemia and cystic fibrosis tend to develop pancreatic cancer at a younger age, but are usually identified with these genetic abnormalities early in life, providing an opportunity for screening. Genetic testing is currently available for BRCA2 and CDKN2A-p16. Carriers of the BRCA2 mutation carry approximately a 7% risk of developing pancreatic cancer by age 80 [11]. In addition, there is a 17% risk of developing pancreatic cancer for carriers of p16 mutations [12]. Germline mutations are carried by 0.6% of patients with familial melanoma. However 58% of these carriers develop pancreatic cancer, while 39% develop melanoma [9]. Furthermore, the risk of developing pancreatic cancer increases to 90% for carriers of CDKN2A who have ever smoked compared to never-smokers, demonstrating the influence of environmental factors on genetic susceptibility [9]. Identification and education of patients who carry such germline mutations may reduce the incidence and perhaps mortality rate from pancreatic cancer in certain subpopulations,

Pancreatic cancer has entered the gene-sequencing age and familial pancreatic cancer (defined as families with at least two first-degree relatives) is being studied by the Johns Hopkins group. A mutational analysis of tumors has identified a germline mutation in the BRCA2 pathway gene, PALB2, associated with familial pancreatic cancer [13]. The Pancreatic Cancer Genetic Epidemiology Consortium (PANGENE) [14], is currently collecting prospective data on familial pancreatic kindreds using a whole genome scan and linkage analysis. To date this program has screened approximately 30,000 cases and has identified about 2,400 cases with a family history, and has identified the known PRSS1, p16, BRCA2 mutations as well as at least 3 other potential areas in the genome carrying familial pancreatic genes.

In addition, PanScan 1 and 2, both international genome-wide association studies (GWAS), have evaluated thousands of cohorts with case controls and have identified genetic polymorphisms that predispose to development of pancreatic cancer including the ABO gene, CLPTM1L-TERT, and NR5A [15, 16]. These polymorphisms contribute an uncertain percentage to the 70% sporadic cases and 20% sporadic young onset cases of the pancreatic cancer population. However, although there are data established to identify patients with increased susceptibility for pancreatic cancer, some of which may undergo genetic testing, it remains unclear how to manage individuals based on these findings. There is a risk stratification proposed for managing patients at risk for pancreatic cancer [17], however there are currently no uniform consensus management recommendations.

MicroRNA Expression

Even if populations at risk for developing pancreatic cancer can be identified and screening for early detection is implemented, histologic diagnosis is often challenging due to the deep-lying location of the pancreas and heterogeneity of tissue obtained by common biopsy techniques. Dr. Nicholai Schultz presented his research on microRNA expression profiles associated with pancreatic cancer (Abstract #153) [18]. The aim of his work was to define the global microRNA expression pattern in pancreatic cancer as compared with normal pancreas and chronic pancreatitis. In this study, microRNA expression patterns in FFPE tissue blocks from pancreatic ductal and ampullary adenocarcinoma surgical specimens were compared to profiles from chronic pancreatitic and normal pancreas specimens.

The results of this analysis revealed that 83 microRNAs were differentially expressed between pancreatic adenocarcinoma and normal pancreas, whereas 32 microRNAs were differentially expressed between pancreatic adenocarcinoma and chronic pancreatitis. The microRNA signatures for pancreatic and ampullary adenocarcinomas were similar (highly correlated). Five microRNAs (miR-614, miR-492, miR-622, miR-135b, and miR-196) were identified that were able to better discriminate pancreatic and ampullary adenocarcinomas from normal pancreas and chronic pancreatitis [18].

The authors compared their results with a previously reported diagnostic microRNA profile for pancreatic adenocarcinoma [19], which validated mirR196b and miR217, and identified 3 other significant profiles. A more complex least absolute shrinkage and selection operator (LASSO) classifier was implemented as a mathematical model to further differentiate microRNA profiles associated with cancer. The LASSO classifier using 19 microRNAs was found to separate pancreatic

adenocarcinoma from normal pancreas and chronic pancreatitis with 98% accuracy. [18].
These findings were encouraging new diagnostic tools for pancreatic cancer using pancreatic samples without micro-dissection of cancer cells, which may lead to earlier detection, and possibly rendering more patients candidates for curative resection. This technique may be especially useful in patients at higher risk for development of pancreatic cancer, such as those with chronic pancreatitis, familial clusters, or genetic anomalies. However, prospective studies are still needed to evaluate if this panel of microRNAs is a clinically useful for early diagnosis of patients with pancreatic adenocarcinoma.

Molecular Prognostic Nomogram for Resectable Pancreatic Cancer

Even though earlier detection of pancreatic cancer may be possible in the near future, tumor biology will likely determine whether or not a patient will benefit from aggressive therapy. Approximately 80% of patients who undergo curative resection will die of pancreatic cancer, many within 6 months of surgery. In an attempt to define biologically relative phenotypes which may influence patient selection, Dr. David Chang presented a molecular prognostic nomogram for resectable pancreatic cancer, which evaluated the potential clinical utility of biologically relevant molecules as prognostic factors in patients with resected pancreatic adenocarcinomas (Abstract #154) [20]. In this study, aberrant S100A4 calcium-binding protein expression was correlated with survival in 372 patients undergoing curative resection. Using these data, a nomogram using clinicopathological variables and aberrant expression of molecular biomarkers was proposed.
High S100A4 expression was demonstrated to be an independent poor prognostic factor in these patients. This study also took into account previously published data identifying S100A2 as a poor prognostic factor in patients undergoing pancreaticoduodenectomy [21], and found that high expression of S100A4 was still an independent prognostic factor [20]. Aberrant expression of these proteins were stratified into three distinct prognostic groups and integrated into a proposed nomogram for selection of patients for surgery.
Other variables that were incorporated into the nomogram included factors that could be measured preoperatively (tumor size and molecular biomarkers) so that patients who were predicted to benefit from aggressive surgery could be identified prior to undergoing pancreaticoduodenectomy. The data identifying S100A4 and S100A2 as prognostic factors were derived from measurements taken from operative specimens, so the authors demonstrated that S100A4 and S100A2 analyzed with quantitative RT-PCR on tissue obtained from endoscopic ultrasound-guided FNA correlated well with amounts found in resected specimens [20].
The authors concluded that the nomogram derived from clinical and molecular factors measured preoperatively could potentially predict survival better than existing nomograms derived from variables determined after examination of the resected specimen. Although the development and application of such nomograms in routine clinical practice has the potential to improve patient selection for aggressive therapies, and ultimately improve outcome for selected subsets of patients, the potential clinical application is yet to be validated.

Conclusion

Epidemiologic and genetic research has established that there are individuals at risk for developing pancreatic cancer. Genetic susceptibility appears to be heterogeneous and currently limited genetic testing is available. Risk stratification is possible, but screening for pancreatic cancer remains a controversial subject for future research. Identification of patients at increased risk may result in implementation of more aggressive screening. Earlier histologic diagnoses may be facilitated as investigators have identified differences in patterns of microRNA expressions between surgical specimens from pancreatic adenocarcinomas containing both tumor cells and surrounding desmoplasia compared to normal pancreatic and chronic pancreatitis specimens. Although earlier detection may render a higher proportion of patients amenable to curative resection, prospective studies are needed to evaluate the clinically usefulness of this technique for early diagnosis. Even if pancreatic cancers can be detected early, clinically and biologically prognostic phenotypes have not yet been defined for pancreatic cancer. Investigators have attempted to derive nomograms using clinico-pathological and molecular biomarker variables to improve patient selection for aggressive therapies. However, potential clinical application is yet to be validated.
The oral presentations at 2011 ASCO GI Cancer Symposium demonstrate advances in identifying prognostic and predictive markers in pancreatic adenocarcinoma that may provide further insight into the future of identification of patients at risk, more aggressive screening for those at increased risk, and earlier diagnosis leading to earlier intervention. Steps toward improved selection for personalized treatment strategies using validated prognosticators may also improve outcome for patients with this devastating disease in the future.

Conflict of interest The authors have no potential conflict of interest

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