HIGHLIGHT ARTICLE

Therapeutic Tools in Pancreatic Cancer
Highlights from the "2009 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 15-17, 2009

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Summary

Pancreatic cancer is the fourth leading cause of cancer death in the United States and has a lower survival rate than other digestive tract tumors. It remains a therapeutic challenge with limited active agents. Honing our current understanding of markers of toxicity and response, and individualizing treatment with the prognostic and therapeutic tools available are important to make a worthy impact on a patient's course. The authors summarize selected abstracts from the ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, USA, January 15-17, 2009. The Symposium featured pancreatic cancer in 84 research abstracts, of which, seven are reviewed that focus on markers of toxicity: cytidine deaminase (Abstract #151) and haptogloin (Abstract #167) as markers of gemcitabine toxicity; markers of response: use of PET scan for prognosis (Abstract #157), and correlations with CA 19-9 to post-chemo-radiation resectability (Abstract #215) and time to progression (Abstract #160); and individualized applications: characterizing the phenotypic similarities between a patient tumor and the direct xenograft (Abstract #154) and a report about the poor outcome of patients with ascites (Abstract #220). Validated clinical tools that can assist in managing patients through the narrow therapeutic window are needed.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States [1] and remains a diagnostic and therapeutic challenge. The chances for achieving five-year survival are best with early diagnosis and treatment, though odds are still slim. Effective early detection and screening for average-risk populations are currently not available. Anatomically, the pancreas is different from other tubular parts of the gastrointestinal tract in that the retroperitoneal space is more difficult to access, sample, and image. Thus, most patients present with advanced disease at diagnosis with a median expected survival with best supportive care of 3-4 months. Symptom control is the focus of treatment and decision to recommend cytotoxic therapy is largely based on performance status. Existing clinical markers of pancreatic cancer lack specificity,

as they are also found in inflammatory diseases of the pancreas and biliary tract. Better clinical tools that can assist in managing patients through the narrow therapeutic window are needed. The "2009 ASCO GI Cancers Symposium" featured pancreatic cancer in 84 research abstracts, of which we review seven that focus on markers of toxicity, response, and individualized therapy (Table 1).

I. Markers of Toxicity (Table 2)

Gemcitabine is a pyrimidine antimetabolite prodrug that requires cellular uptake. It is either inactivated by cytidine deaminase (CDA) to difluorodeoxyuridine (dFdU), otherwise it is activated by deoxycitidine kinase (dCK) where the nucleotide metabolite difluorodeoxycytidine 5'-triphosphate (dFdCTP) is incorporated into DNA resulting in chain termination. dCK is the rate-limiting enzyme for the activation pathway, and a patient's phenotypic expression may play an important role in response to gemcitabine therapy [2, 3]. Similarly, CDA expression is instrumental for inactivation and may play an important role in gemcitabine toxicity.

The hypothesis that there is an association between tumor dCK expression and outcome has been evaluated in clinical trials of pancreatic cancer patients. Sebastiani and colleagues showed dCK protein expression from human pancreatic adenocarcinomas varied in immunohistochemistry labeling intensity [4].

Table 1. Selected abstracts for this highlights review of the 2009 ASCO GI Cancers Symposium that describe therapeutic tools or markers to help better understand treatment categories, toxicity, or response and prognosis in patients with pancreatic cancer.

Abstract	Author	Tool/marker	Utility	Title
#151 [8]	Dahan, *et al.*	CDA phenotype	Marker of toxicity	A simple test to anticipate severe toxicities upon gemcitabine intake
#154 [23]	Vinjamaram, *et al.*	Patient tumor xenograft	Advancing individualized therapy	Direct patient tumor xenograft prototype for drug testing and individualizing chemotherapy in pancreatic cancer
#157 [11]	Schellenberg, *et al.*	[18]FDG-PET	Marker of response	Using PET scan parameters to predict survival in locally advanced pancreas cancer
#160 [16]	Boeck, *et al.*	CA 19-9	Marker of time to progression	Application of a time-varying covariate model to the analysis of CA 19-9 as a biomarker for time to progression in patients with advanced pancreatic cancer
#167 [9]	Matsubara, *et al.*	Haptoglobin	Predict hematologic toxicity	Identification of a predictive biomarker for hematological toxicities of gemcitabine
#215 [18]	Rault, *et al.*	CA 19-9	Marker of resectability	Use of post radiochemotherapy levels of serum CA 19-9 to predict resectability for patients with locally advanced pancreatic adenocarcinoma
#220 [21]	Shimizu, *et al.*	Malignant ascites	Individualize treatment recommendations	Treatment efficacy and prognostic factors of gemcitabine for advanced pancreatic cancer with malignant ascites.

CA 19-9: carbohydrate antigen 19-9; CDA: cytidine deaminase; [18]FDG: ^{18}F-fluorodeoxyglucose; PET: positron emission tomography

They found that low intensity staining of dCK correlated significantly with both overall survival and progression-free survival when these patients were treated with gemcitabine based therapy.

Similarly, CDA mutations and phenotype have been implicated in anticipating gemcitabine toxicity. Sugiyama et al reported on polymorphisms that could be associated with gemcitabine toxicity in their patients [5]. Others have suggested that rather than mutations, CDA phenotype is perhaps a better predictor of toxicity, and mutations can lead to false negatives [6, 7].

Dahan *et al*. in Abstract #151 [8] report on a phenotypic test of CDA activity towards anticipating those at risk for gemcitabine toxicity. They evaluated baseline CDA phenotypes of 130 patients receiving gemcitabine in retrospective fashion and found large variability in CDA levels with a mean of 3.6±2.8 U/mg. Contrary to Sugiyama *et al*. [5] and other reports on genotypic correlations with toxicity, Dahan *et al*. found a trend of lower CDA levels with increased toxicity (P values were not reported). They did not find mutations of the CDA gene to be prognostically relevant for toxicity.

Matsubara *et al*. (Abstract #167) [9] focused on finding a test that would predict hematologic toxicity in patients with pancreatic cancer receiving gemcitabine. They used a case-control approach to evaluate the plasma proteomes of 47 patients divided into two cohorts of those without hematologic toxicity (grade 0), and those with grade 3-4 neutropenia and/or grade 2-4 thrombocytopenia. Using quantitative mass spectrometry, they found 757, 1.2% out of 60,888 peptide peaks sampled, that were significant (P<0.001). Out of these, haptoglobin was the marker found to have the lowest P value, and they argue, most statistically significant. They used haptoglobin in addition to neutrophil and platelet counts, body surface area, in a forward stepwise goodness-of-fit model to develop a nomogram which they prospectively studied in two independent validation cohorts of patients with pancreatic cancer. They found that baseline absolute neutrophil count and serum haptoglobin levels were statistically significant (P=0.0003 and P=0.031, respectively) with odds ratios (OR) of 0.72 and 0.71, in predicting grade 3-4 neutropenia or grade 2-4 thrombocytopenia, respectively. The authors do not specifically include a range of haptoglobin or neutrophil values that they determine to correlate, nor do they comment on other scenarios or clinical findings in their patients that would account for altered haptoglobin levels (such as intravascular hemolysis, or fucosylated haptoglobin[10]).

II. Markers of Response (Table 3)

Positron emission tomography (PET) scan is not a routine part of staging for pancreatic cancer. There are situations where it may be obtained, such as post-resection rising CA 19-9 with soft-tissue changes in the surgical bed seen on CT, or with equivocal or indeterminate findings in the liver or lung. The caveat is ^{18}F-fluorodeoxyglucose (FDG) is often not detected in disease that is less than 1 cm. Schellenberg *et al.* (Abstract #157) [11] correlated baseline PET scan

Table 2. Markers of toxicity in patients with pancreatic cancer receiving gemcitabine based therapy.

Abstract	Tool/marker	Clinical utility	No.	Design	Comments
#151 [8]	CDA phenotype - screen	Anticipate gemcitabine toxicity	130	Observational, retrospective	Do not clearly define toxicity measurement
#167 [9]	Baseline haptoglobin	Anticipate gemcitabine neutropenia or thrombocytopenia	47	Case control followed by two validation cohorts	Not clear if the authors control for fucosylated haptoglobin or other scenarios for intravascular hemolysis

CDA: cytidine deaminase

Table 3. CA 19-9 and PET scan as potential markers of response in patients with pancreatic cancer.

Abstract	Tool/marker	Clinical utility	No.	Design	Comments
#157 [11]	[18]FDG-PET	Baseline PET to assess prognosis in locally advanced disease treated with chemo-radiotherapy	56	Retrospective	Single radiation oncologist determined treatment volumes. Institution developed software for calculation of mSUV and MTB
#160 [16]	CA 19-9	Time to progression in advanced pancreatic cancer	115	Retrospective	Baseline CA 19-9 and trend during therapy may have an impact in predicting time to progression
#215 [18]	CA 19-9	Decision for resectability in post chemo-radiotherapy patients with locally advanced disease	27 evaluable	Retrospective	12 of 27 patients that were surgically explored had a complete resection with clear margins

[18]FDG: ^{18}F-fluorodeoxyglucose; CA 19-9: carbohydrate antigen 19-9; mSUV: maximum standard uptake value; MTB: metabolic tumor burden; PET: positron emission tomography

Table 4. Abstract #157 found baseline PET scan values of mSUV and MTB to independently predict length of survival in patients with locally advanced pancreatic disease [11].

Cohort	Median survival (months)	P
Maximum standard uptake value (mSUV: Hi *vs*. Lo)	10.5 *vs*. 16.8	0.02
Metabolic tumor burden (MTB: Hi *vs*. Lo)	10.5 *vs*. 18.7	<0.01

parameters with overall survival in locally advanced pancreatic cancer. They used open source software (developed at their institution and available for download at http://rtimage.sourceforge.net/index.html [12]) for measuring maximum standard uptake value (mSUV) and metabolic tumor burden (MTB) of baseline PET scans in 56 patients with locally advanced pancreatic cancer [13, 14]. Median survival was 12.7 months for all patients. They divided patients into two cohorts of high and low mSUV, and high and low MTB, and found significant differences between these groups (Table 4). When they further divided the patients into 4 subgroups of high and low mSUV and MTB, they found that the patients with both low MTB and mSUV had median survival of 18.7 months compared to the median survival of 9.3 months of the group that had high MTB and mSUV (P=0.058).

CA 19-9 is not specific for pancreatic cancer and may be elevated in other GI tumors, however it is the most commonly elevated serum tumor marker in pancreatic cancer [15]. The serum value corresponds to the CA 19-9 antibody response to the carbohydrate moiety of mucin 1 (MUC1). Decision for its use is based on mostly retrospective data, and it is still unclear if or how it should be used for prognosis, staging or pre-operatively as an independent predictor of resectability. Boeck *et al.* (Abstract #160) [16] sought to analyze time to progression based on baseline *versus* trend of CA 19-9 in their multicenter retrospective analysis of non-resectable pancreatic cancer patients. They

included 115 patients with confirmed pancreatic cancer and a pre-treatment CA 19-9 of at least 5.2 U/mL. Nearly 90% had metastatic disease, and most were treated on a clinical trial. Median time to progression was 4.4 months and univariate and multivariate analysis showed a significant (all P values <0.001) correlation of time to progression and pre-treatment CA 19-9 and CA 19-9 trend on treatment.

In 2003, Wolff *et al.* retrospectively examined pre-gemcitabine/radiation levels of CA 19-9 in 79 resectable patients and found that patients with a CA 19-9 level of greater than 668 U/mL predicted radiographic presence of metastasis or early relapse [17]. Rault *et al.* (Abstract #215) [18] examined neoadjuvantly treated CA 19-9 values to predict resectability. Retrospectively, 33 patients with histologically confirmed pancreatic cancer were evaluated post-chemoradiation and 27 were surgically explored. Of this surgical cohort, there was a 2:1 ratio of patients with CA 19-9 less than 200 U/mL. Fifteen were able to have a pancreatic resection, for a more favorable resectability rate in patients with CA 19-9 less than 200 U/mL by a nearly 3:1 margin.

III. Individualized Therapy (Table 5)

Ascites in pancreatic cancer occurs in approximately 20% of patients and can be attributed to increased production of tumor exudates, osmotically active peptides that perturb vascular permeability, or obstruction of diaphragmatic lymphatics [19]. When it occurs ascites is usually the final manifestation, and it need not be proven to be malignant cytologically [20]. However, it is not clear if the amount of ascites matters. Shimizu *et al.* in Abstract #220 [21] performed a retrospective review of 80 patients with malignant ascites treated with gemcitabine, and looked for efficacy in cohorts of patients noted as having minimal, moderate, or massive ascites. Median survival was 4.2 months. Quality of life measures were not reported,

Table 5. Validation for preserved phenotypic markers in patient tumor xenografts is an important step toward applying theragnostics in pancreatic cancer. More options for patients with ascites are needed.

Abstract	Tool/marker	Clinical utility	No.	Design	Comments
#154 [23]	Patient tumor - xenograft	Toward theranostics - choose the optimal drug for the patient's tumor	15	Retrospective	Histology, E-cadherin, and c-kit are preserved in their xenograft models.
#220 [21]	Malignant ascites	Choice of therapy	80	Retrospective	Ascites carries a poor prognosis in pancreatic cancer and should be considered in therapy decisions

Table 6. From abstract #154: Percent that retained surgical specimen characteristics through first and second passages in severe combined immunodeficiency (SCID) xenografts (formalin fixed, paraffin embedded tissue) [23].

Passage	Maintained histology	Immunohistochemistry staining			
		E-cad	c-kit	Fibronectin	Vimentin
Surgical specimen	Baseline	92%	85%	71%	1 spec. only
1st passage	Not reported	92%	76%	64%	Staining lost
2nd passage	61% same	100%	69%	41%	Staining lost

though improvement in ascites was noted in 17.5% with a median time to treatment failure of 1.6 months. A multivariate analysis did show that amount of ascites, as well as performance status, were independent prognostic factors.

It is clear that more progress is needed in drug development for pancreatic cancer. Direct tumor xenografts can be used to test therapeutic approaches in pancreatic cancer; in fact, the model was recently used as a platform to advance targeting the pancreatic cancer stem cell [22]. An advantage is that all cellular fractions of the tumor can be evaluated; not just the tumor. However, it is not clear how well represented the patient's tumor is in a mouse xenograft that has undergone some necessary processing in the lab, including passaging once or twice, for nude mouse implantation. Vinjamaram *et al.* (Abstract #154) [23] compared the histologic grade and immuno-histochemistry staining of E-cadherin, c-kit, and other markers in the patient's surgical specimen with that of first and second passages that were used as xenografts in severe combined immunodeficiency (SCID) mice. The specimens were formalin fixed and paraffin embedded for processing. They found that histologic grade was preserved between patient and the passaged cells. Staining for E-cadherin and c-kit was preserved through the passages, however, this was not true for fibronectin and vimentin (Table 6).

Conclusion

Better clinical markers can be beneficial for selecting patients for therapy, timing of therapy, and understanding prognosis of individual patients. With further study and validation, it is possible some of these tools make their way into randomized clinical trials and help advance therapy.

Conflict of interest: The authors have no potential conflicts of interest

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