Pancreatic Cancer

Recent Progress and a Look Forward

Pancreatic Adenocarcinoma

- Highly lethal tumor
- 2% of All Cancer Cases
- 5% of All Cancer Deaths
- 4th Leading Cause of Cancer Death
  - Lung
  - Colorectal
  - Breast
  - Pancreas

Pancreatic Adenocarcinoma

- Cure is rare and only seen in resected patients.
- 100 Patients:
  - 15 - 20 patients will have resectable tumors.
  - Of these, 1 in 5 have long-term survival.
  - 3 - 4% five year survival.
- Tumors are resistant to chemotherapy and radiation.
  - The mechanism(s) of resistance are diverse.
- Survival for most patients is measured in months.
- Primary prevention is paramount!

Pancreatic Cancer Risk Factors

Environmental

- Cigarette smoking (~25%)
- ETOH/chronic pancreatitis

Metabolic (>25%)

- Diabetes
- Obesity

Genetic

- Pancreatic cancer families
- Hereditary syndromes

Mucinous pancreatic cysts

- Mucinous Cystic Neoplasm
- Intrapancreatic mucinous neoplasm (IPMN)

Recent Translational Progress

- Initial histologic and molecular characterization of precursor lesions.
- Initial descriptions of mutational profile of pancreatic cancer.
- Development of GEMMs and patient-derived xenografts (PDX).
- Importance of tumor-related stroma (stellate cells & immunocytes).
- Recognition of the role of diabetes and obesity in pancreatic cancer risk and survival.

Recent Clinical Progress

- Initial screening efforts for patients with FPC or known germ-line mutations conferring risk.
- Understanding the natural history of mucinous cystic neoplasms and development of criteria for surgical resection.
- Recognition that development of targeted agents will require understanding pancreatic cancer cellular heterogeneity.
- Effective integration of currently available modalities (surgery, radiation, chemotherapy).

CTAC Pancreatic Cancer Working Group

Purpose: Develop strategies and recommendations that will advise NCI on ways to reduce the incidence and mortality rates of adenocarcinoma of the pancreas.

Goals:

- Develop strategies to increase the extent of collaboration between centers studying pancreatic cancer. This may include:
  - Increasing tissue acquisition in association with high-quality clinical data to facilitate greater genetic and biochemical characterization of the disease;
  - Assessing recent progress in the field;
  - Scanning the horizon for future developments in medical science.
- Developing recommendations to capitalize on new investment opportunities.
- Provide advice on the NCI plan to implement the recommendations.

Pancreatic Cancer: Scanning the Horizon for Focused Interventions

October 23-24, 2012

Critical Questions - Areas of Greatest Need

- Can we identify cohorts of individuals at high risk?
- Can we screen patients deemed to be at high risk and identify pre-invasive pathologic precursors or very early cancer?
- Can we develop effective systemic therapies?

Other Provocative Questions

Why does pancreatic cancer occur in some patients with no known risk factors or genetic abnormalities?

Why do identical mutations (e.g. CDKN2A) result in pancreatic cancers in some patients and melanoma in others?

Can aspirin and/or metformin prevent or control pancreatic cancer?

Why do some patients with pancreatic cancer respond remarkably to treatment while most others do not?

Breakout sessions

- Epidemiology and Risk Assessment Research
- Pathology, Screening and Early Detection Research
- Therapeutic Research

Develop Precise Near-term Goals

- Are we in a position to test the clinical usefulness of available biomarkers to risk-stratify patients deemed at moderate risk based on clinical criteria?
  - New-onset diabetes
  - Obesity/metabolic syndrome
  - Mucinous cystic neoplasms
- What can be done to improve the screening of patients with high risk germ-line mutations or pancreatic mucinous cysts that are precursors to invasive pancreatic cancer?

Develop Precise Near-term Goals

- Can we specify efficacy criteria that should be generated during pre-clinical testing of a novel therapeutic before testing the agent in patients with advanced pancreatic cancer?
- Using available model systems can we precisely identify the molecular or biochemical characteristics of the pancreatic cancer patient population likely to respond to the targeted intervention in the clinic?

High Level Recommendations

Two patient populations can currently be broadly defined that are at increased risk for pancreatic cancer:

1) New-onset diabetics
   - **Develop a means to identify the approximately 1/125 patients with new-onset diabetes who have early pancreatic cancer.**

2) Patients with specific germ-line mutations, familial pancreatic cancer, or mucinous pancreatic cysts
   - **Develop screening methods to identify those patients with heritable pancreatic cancer (specific germ-line mutations or pancreatic cancer families) or mucinous pancreatic cysts (MCN and IPMN) who will progress to invasive pancreatic cancer and require (surgical) intervention.**

High Level Recommendations

3) Develop strategies that neutralize the driver oncogene KRAS.

4) Accelerate clinical and preclinical therapeutic approaches that target the immune and non-immune components in pancreatic tumors.

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- Comments and Discussion regarding the pancreatic cancer initiative.

- **Additional Discussion:**

  Are there other cancers or cancer properties (e.g. metastasis or genomic instability) that could benefit from focused attention by a working group?