Treatment Approaches in Pancreatic Cancer

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Detroit

Karmanos Cancer Center
NCI-designated comprehensive cancer center
Outline

• Background information
• Current treatment approaches
• The hope of targeted therapies
• Providing comprehensive care
• Concluding remarks

Fighting pancreatic cancer

• Expanding our basic knowledge of the disease
• Applying the new science in the development of new and effective therapies
• Providing patients with access to clinical trials using new drugs
• Providing patients a high level multidisciplinary care
A Major Challenge

Not diagnosed at an early stage!

The Pancreas

© D Klemm '98
Pancreatic cancer

- The vast majority of patients diagnosed with pancreatic cancer have micro- or overt metastatic disease
- Improvements in outcome in patients with pancreatic cancer will depend on developing better drug (systemic) therapies
What makes pancreatic cancer an aggressive cancer?

• The cancer cells can travel to other parts of the body
• The cancer cells are somewhat resistant to conventional drug therapies and radiation

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## Treatment options based on disease stage

<table>
<thead>
<tr>
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<th>Treatment</th>
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<tbody>
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<td>Localized and vessels free</td>
<td>Radical resection +/- chemotherapy/radiotherapy</td>
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## Chemotherapy is needed in almost every patient with this disease

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Almost everyone with pancreatic cancer needs drug therapy, even those with early disease.

Increasing availability of drugs to treat pancreatic cancer:

- Gemcitabine (Gemzar)
- Erlotinib (Tarceva)
- Nab-paclitaxel (Abraxane)
- FOLFIRINOX
Remissions on FOLFIRINOX
patient #1

Before

After

Remissions on FOLFIRINOX
patient #2

Before

After
Side effects to drugs: Milder treatments

- Gemcitabine (Gemzar)
  - Low blood counts
  - Fatigue
  - Leg swelling

- Erlotinib (Tarceva)
  - Skin rash
  - Diarrhea

Side effects to drugs: more intense treatments

- FOLFIRINOX
  - Nausea with or without vomiting
  - Diarrhea
  - Fatigue
  - Effect on blood counts
  - Infection
  - Neuropathy

- Gemcitabine/nab-paclitaxel (Abraxane)
  - Fatigue
  - Effects on blood counts
  - Nausea with or without vomiting
  - Neuropathy
# Advanced pancreatic cancer: Systemic treatment options

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**What are the challenges with the conventional “chemo”?**

- Less specific against cancer cells (also affects normal cells)
- Side effects
- Cancer cells develop resistance (immunity) to these drugs

**What is needed?**

- A better understanding of what causes resistance to drugs
- Discovery of better drugs that have specific targets
- Personalizing therapies
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Era of Targeted Therapies
Disease behavior dictated by genetic mutations in the tumor

Complexity of genetic mutations in pancreatic tumors

- 20,661 genes
- Average 63 alterations per patient
- Mostly point mutations

Jones et al, Science, September, 2008
Cancer Genes: the “good” and “bad ones”

- **Bad genes**
  - Oncogenes
  - Push the cell to divide, spread and dodge treatments
  - Examples: Her-2, KRAS

- **Good genes**
  - Tumor suppressor genes
  - Put the brakes on cell division and spread
  - Examples: p53, p16

**How to target?**

- Disrupting a signaling cascade within the cancer
- Cutting off blood supply to tumor
- Regaining the function of the “good” or tumor suppressor genes
Redundancies and Cross Talks


Redundancies of signaling pathways: Where to block?
Drug combinations or cocktails

- Hitting multiple targets in the cancer cell simultaneously
- Preventing the emergence of drug resistance
- Success in HIV disease and in other cancers
Randomized Phase II Clinical Trial of AZD6244 (Selumetinib) and MK2206 vs. mFOLFOX in Patients with Metastatic Pancreatic Cancer after Prior Chemotherapy

**SWOG 1115**

Dr. Vincent Chung
City of Hope
*Young Investigator*

**MEK & Akt dual “downstream” blockade**

Proliferation
Drug resistance
Angiogenesis

Targeting Nuclear Export Protein CRM-1 in Pancreatic Cancer using KPT-330

CRM-1 is the major protein exporter of tumor suppressor proteins

- Nuclear localization of Tumor Suppressor Proteins (TSPs) is key to their surveillance activity
- Cancer cells suppress TSP function through their constant export utilizing CRM-1
- Elevated CRM-1 expression has been correlated with poor prognosis in different cancers and is considered a driver of chemotherapy resistance
Nuclear Transport Machinery

Attacking the cancer cell is NOT enough

Must also destroy the neighborhoods that hide and support the bad cells!
Stromal influence on pathogenesis and progression

Olson and Hananhan, Science, 324:1400-1401, 2009

Stromal compartment is a new target

Olson and Hananhan, Science, 324:1400-1401, 2009
Hyaluronan (HA) as a target in Pancreatic Cancer:

• HA overexpression in > 80% of pancreatic cancers
• Tumors that accumulate HA develop high interstitial fluid pressure and drug resistance
• HA is associated with disease progression and poor prognosis

A PHASE IB/II RANDOMIZED STUDY OF MODIFIED FOLFIRINOX + PEGYLATED RECOMBINANT HUMAN HYALURONIDASE (PEGPH20) VERSUS MODIFIED FOLFIRINOX ALONE IN PATIENTS WITH GOOD PERFORMANCE STATUS METASTATIC PANCREATIC ADENOCARCINOMA

S1313

Ramesh Ramanathan
in collaboration with Halozyme
Targeting the stem cells in the tumor

Finding and removing the needle in the haystack
Normal → Cancer Stem cell

Tumor proliferation
Detect the SC before it forms a tumor.

Tumor proliferation:
- Normal
- Cancer stem cell

Treatment:
- If treatment fails, it results in relapse.

CURE!
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Patients with pancreatic need a comprehensive multidisciplinary care

• Symptom management
  – Pain
  – Nutrition
  – Depression
• Requirements for multiple forms of therapies
  – Drugs or chemo
  – Surgery
  – Radiation
• Psychosocial support
Research and Clinical Trials

Only 4% of patients are enrolled in clinical trials in the USA
A mouse carrying a cancer is not the same as a patient with cancer

Status of clinical trials in pancreatic cancer: a PanCan analysis
Pancreatic cancer clinical trials open in United States in 2011 and 2012 by phase.

Most available clinical trials are in advanced disease

Hoos W A et al. JCO 2013;31:3432-3438
Most clinical trials are using targeted agents

More trials are available in larger cities in the US
The 133 pancreatic cancer–specific clinical trials open in United States in 2011 were identified by sponsor indicated in clinicaltrials.gov.

Specific research strategies at Karmanos

- To identify why pancreas cancer cells are resistant to therapy
- To develop molecular techniques that would explain the processes for resistance in a given patient
- To design treatments that would overcome drug resistance
- To take advantage of the highly integrated pancreas cancer care delivery system at Karmanos and national research collaborations

Hooe W A et al. JCO 2013;31:3432-3438
SUMMARY

• Newer drugs starting to improve the outcome of patients with pancreatic cancer
• New treatments are being developed that are based on advances in science
• Patients must be encouraged to participate in clinical trials
• Need for personalized therapies
Questions