Treatment Approaches for Pancreatic Cancer: Hope on the Horizon

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Disclosures

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Outline

• Background
• Surgery
• Medical Therapy
  – Post-surgery (adjuvant therapy)
  – Locally advanced
  – Metastatic
• New Trials and New Promise

Pancreatic Cancer

• US in 2012
  – 43,920 new diagnoses
  – 37,390 deaths

• Worldwide in 2008
  – 278,684 new diagnoses
  – 266,669 deaths
Risk Factors

- Tobacco and Alcohol Use
  - Minor
- Genetically Inherited (<5%)
  - BRCA1 & 2
  - PALBB2
- Other Causes
  - Chronic Pancreatitis
  - Toxins (very, very rarely)
  - Race?
  - Diet?

Symptoms

- Abdominal pain
- Weight loss
- Jaundice/Biliary Obstruction
- Fatigue
- Dyspepsia
- Diabetes Mellitus
Difficulties in Assessment

- Subtle symptoms
- Hard to visualize
  - CT vs. MRI
  - Endoscopic ultrasound
  - Unclear role of PET scans
- Nature of spread/metastases
  - Ascites
  - Lymph nodes
  - Local spread/invasion
  - Distant metastases

Can We Diagnose it Earlier?

- No evidence for CTs, MRIs, EUS, etc
  - *Not even in the rare families with inherited pancreatic cancer*
- Is there a blood test?
  - *Ca 19-9 is not a useful screening tool*
  - Serum microRNA? Metabolomics?
Pancreatic Cancer Staging

- **Stage I:**
  - IA: T1, N0
  - IB: T2, N0
- **Stage II**
  - IIA: T3, N0
  - IIB: T1-3, N1
- **Stage III:** T4, N any (locally advanced, unresectable)
- **Stage IV:** T any, N any, M1

- **Primary Staging is Resectable vs. Unresectable**
  - **Secondary – Locally Advanced vs. Metastatic**

Pancreatic Cancer Statistics

- Pancreatic cancer can be a deadly disease
- **At diagnosis**
  - Only 20% are operable
  - 20% are inoperable, locally advanced
  - 60% are metastatic
- **For the 10-20% who are operable**
  - 80% will recur
  - 20% will be cured (<5% overall)
Surgical Definitions

• Whipple Procedure for head/body of pancreas tumors
  – Removes head and body of pancreas, duodenum, part of stomach (sometimes), gall bladder (usually)
  – Major operation – 4-6 week recovery
  – Change in digestion (“plumbing”) after
  – “Lap-assisted” Whipple – revolutionary

• Distal pancreatectomy – for tail of pancreas tumors
  – Removes tail of pancreas
  – Spleen (shared blood supply)
  – Less-major operation ~4 weeks of recovery
  – Laparoscopic distal pancreatectomies

Surgical Definitions

• Common surgical principles
  – Assessment of vasculature
    • Tumors involving arteries might not be remove-able
    • Tumors involving veins – more controversial
  – Assessment of peritoneum and liver
  – Removal of tumor with good “margins”
  – Removal of local lymph nodes
Recovery from Surgery

- Usually takes 4-6 weeks
- Often includes surgical drains
- Infections can occur
- Adjusting to new “plumbing”
- Patients often lose 10-20% of their body weight (forever)

Medical Therapy: Outline

- Post-operative
  - “Adjuvant”
  - Decrease rates of recurrence = increased cure
  - “Neoadjuvant”
- Locally Advanced
  - “Conversion” therapy
  - Slow development of metastases
  - Extend survival
  - Maintain quality of life
- Metastatic
  - Extend survival
  - Maintain quality of life
Post-Operative Therapy

- Only 20% of *operative* patients are cured
  - Average survival ~24 months

- 80% chance of recurrence after surgery
  - Local and systemic recurrence

- Pancreas cancer “seeds” very early
  - Can we kill those seeds?
Post-Operative Chemotherapy

- **Clear benefit**
  - Prolonged survival
  - Decreased recurrence = increased cure
- **Examples**
  - ESPAC-1 (5-Fluorouracil vs. observation)
    - Average survival: 20 vs. 15 months
    - % 5 year survival: 21 vs. 8%
  - CONKO-001 (Gemcitabine vs. observation)
    - Average survival: 22 vs. 20 months
    - % 5 year survival: 17 vs. 6%
Post-Operative Chemotherapy

- **What kind of chemotherapy**
  - ESPAC-3: Gemcitabine vs. 5-Fluorouracil
  - Average Survival: 23.6 vs. 23 months

- **Benefit of radiation?**
  - Not clear
  - Radiation (with a low dose of oral 5-Fluorouracil) for 4-6 weeks after chemotherapy

Neoadjuvant Therapy

- **For patients with resectable disease**
  - Prior to surgery
  - Chemotherapy +/- radiation

- **Are we just selecting patients out?**
  - Overall survival still ~24 months
  - 30% of patients – surgery not appropriate
    - Patients become ill
    - Cancer grows/spreads before surgery
  - Of the remaining 70%
    - Improved overall survival
    - 30-34 months

- **Highly debated topic**
  - Should be pursued as a randomized trial
Locally Advanced Disease

Definitions
Respectable vs. Unresectable: Definitions Vary

- **Resectable disease**
  - No involvement with local blood vessels
- **Borderline resectable disease**
  - Abutment (<180°) of the local arteries
- **Unresectable disease**
  - Encasement (>180°) of the local arteries
- **Involvement of the veins** – greater variation

Locally Advanced Cancer

- **Chemotherapy PLUS Radiation**
  - Clearly improves survival over radiation alone
  - Average survival ~12 vs. 6 months
- **Is radiation necessary?**
  - Controversial due to mixed results
Locally Advanced Cancer

• Sequence of therapy?
  – Radiation first
    • ~30% will develop metastases just after radiation
  – Chemotherapy first
    • ~30% will have growth of the primary mass, even if there are no metastases

• Type of radiation?
  – Traditional or IMRT?
  – Stereotactic radiation?

Disease “Conversion”

• Making unresectable disease → resectable
  – Only occurs in 10-20% of patients (at most)

• Choice of chemotherapy?
  – Better outcomes with FOLFIRINOX?

• Choice of radiation?
  – Traditional or IMRT vs. Stereotactic radiation
Metastatic Disease

Metastatic Cancer: Pre-2011

• Average survival
  – No treatment 2-4 months
  – With chemotherapy 6-8 months
  – 1 year survival rate ~ 20%

• Goal of therapy
  – Extend survival
  – Improve symptoms
Metastatic Cancer: Pre-2011

• Gemcitabine
  – Very well tolerated
  – Initially approved based on an improved quality of life

• Survival benefit vs. 5-Fluorouracil
  – Average survival 5.7 months vs. 4.4 months
  – 1 year survival 18% vs. 2%

Combination Chemotherapy?

• No chemotherapy with gemcitabine had been proven to be superior to gemcitabine alone in survival
  – 5-FU/capecitabine
  – Oxaliplatin/Cisplatin
  – Irinotecan
  – Pemetrexed

• Example: Gem + Oxaliplatin vs. Gem alone
  – Increased response rate with Gem + Ox
  – BUT survival rates the same

• What about targeted therapies?
Only One Targeted Therapy

- Gem vs. Gem + erlotinib – Phase III
- Average survival 6.37 months vs. 5.91 months
  - .46 months = 14 days
- 1 year survival 24% vs. 17%

New Standards – Post-2011

- FOLFIRINOX vs. Gemcitabine - Phase III
  - RR: 31% vs. 9%
  - OS: 11.1 vs. 6.8 mos
  - Moderate toxicity
New Standards – Post-2011

- Gemcitabine + nab-paclitaxel vs. Gemcitabine
  - Phase III
  - Well tolerated

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Survival</th>
<th>Progression Free Survival</th>
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<tbody>
<tr>
<td>Gemcitabine</td>
<td>6.7 months</td>
<td>3.7 months</td>
</tr>
<tr>
<td>Gemcitabine/nab-Paclitaxel</td>
<td>8.5 months</td>
<td>5.5 months</td>
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- HR=0.72, P=0.000015
- HR=0.69, P=0.000024

- 22% 1-year Survival
- 4% 2-year Survival
- 7% Overall Response Rate
- 33% Stable Disease

- 35% 1-year Survival
- 9% 2-year Survival
- 23% Overall Response Rate
- 48% Stable Disease

New Hope on the Horizon

Clinical Trials in Pancreatic Cancer

Von Hoff, et al. ASCO, 2013
**Metastatic → Earlier Stage**

- Can we apply metastatic regimens to localized disease
  - Locally advanced/borderline resectable
    - Increase rate of resectability
    - Pre-op FOLFIRINOX or Gem + nab-paclitaxel
  - Adjuvant therapy
    - Increased eradication of micrometastatic disease
    - Adjuvant FOLFIRINOX or Gem + nab-paclitaxel

**Improved Local Therapy**

- Stereotactic radiation
- Irreversible electroporation
- Liver-directed therapy
New Treatments

• New targets being identified
  – Targeting the cell surface
  – Targeting cell signaling
  – Targeting cell division
  – Targeting the tumor environment
  – Immunotherapy

New Targets: PARP

- Critical DNA repair enzyme (SSB, BER)
- Often overexpressed in cancer cells
- Confers resistance to chemotherapy and radiation

Inhibition of PARP
- Prevents recruitment of DNA repair enzymes
- Leads to failure of single strand break repair

Unrepaired break site \(\rightarrow\) replication fork arrest
- Leads to degeneration into double-strand breaks
- Ultimately \(\rightarrow\) chromosomal catastrophe cell death
Homologous Recombination Deficient Cells Are More Susceptible to PARP Inhibition

- BRCA-1, -2 are critical for DNA repair via HR
- Cells defective in BRCA-1, -2 are more sensitive to DNA-damaging therapy
- Cells defective in BRCA-1, -2 are more sensitive to PARP inhibition
  - Cancer cells unable to repair double-stranded breaks die through apoptosis

Homologous Recombination Deficient Cells Are More Susceptible to PARP Inhibition

- Homologous recombination enzymes are critical for DNA repair
  - Defects in BRCA-1, -2, PALB-B2, FANC → increased sensitivity to DNA-damaging chemotherapy and to PARP inhibition
- BRCA-2 mutations in pancreatic cancer
  - 5 – 17% of pancreatic cancer patients carry BRCA-2 mutations
- Multiple clinical trials of PARP inhibitors
  - Consistent evidence of increased efficacy in BRCA-1 or -2 mutant tumors
  - Anecdotal evidence in pancreatic cancer
    - e.g. Lowery, et al, 2011, MSKCC - 15 patients with known BRCA-1 or -2 mutations
      - 4 patients with PARPi-based therapy
      - 3 PRs and one SD for 6 months
**Preliminary Results**

- **2 patients with defined BRCA mutations**

**Enhancing Anti-Tumor Immunity**

- CTLA-4 is a negative costimulatory molecule
- Blockade of CTLA-4 → T cell activation and proliferation
- 15 – 20% risk of clinically significant inflammatory and autoimmune adverse effects
- The programmed death 1 (PD-1) receptor is also a negative regulator of T cells
- The PD-1 ligand (PD-L1) is expressed by tumor cells directly
- PD-1 inhibition → direct activation of cancer-specific T-cells with much fewer AEs

Enhancing Anti-Tumor Immunity

- Anti-PD-1 and PD-L1 Abs being tested
- Experience limited
  - Some early evidence of activity in pancreatic adenocarcinoma
  - Very few side effects

Tabernero, et al, ASCO, 2013

Patient “Tailored” Therapy

New genomic and proteomic tests provide specific information on cancer behavior

Theranostics Health, Inc: TherALink™ Drug Target Activation Mapping

Foundation Medicine:
- Full Exon Sequencing
- Broad-scale mutation analysis
- Future: Full Genomic Sequencing

Caris, Inc:
- Target Now Assay
- IHC and DNA mutations

Caris Target Now provides the most valuable information for your care.

Caris Target Now helps identify critical targets for personalized treatment.

Georgetown | Lombardi
Patient “Tailored” Therapy

- ESMO, 2013 – Hidalgo’s group
  - Molecular Profiling → Increased Survival
  - Retrospective Review
  - TS and TP were the strongest predictors
  - OS
    - Profiled patients = 12 months
    - Non-profiled patients = 7.6 months

- AACR, 2012 – Ramanathan’s group
  - Prospective study
  - Molecular Profiling → Therapy recommendations in 47 patients
Patient “Tailored” Therapy

- Tumor xenograft model
  - Tumor specimens grown in mice
  - Chemotherapy testing to identify effective treatments
  - Champions Oncology

- Pharmacogenomics model
  - Serum testing of tumor-borne chemosensitivity markers
  - CellPath Therapeutics
Pancreatic Cancer - The Future

• Can we diagnose patients earlier?

• Can we operate on more patients?
  – Preoperative studies – RENDER more patients operable

• Postoperative Therapy
  – Decrease chance of recurrence

• New Therapies
  – We desperately need novel clinical trials

• Personalized Therapy
  – Can we treat each patient with the therapy they need?
  – Can we apply this to the adjuvant/pre-operative setting?

Thank You