Pancreatic Adenocarcinoma: Current Treatment Approaches
Pancreatic Cancer Action Network Seminar
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Rubenstein Center for Pancreatic Cancer Research
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Agenda

• Pancreas cancer epidemiology
• Early stage disease
• Advanced disease
• Clinical trials
• Novel agents in development
The Problem and Challenges

• New diagnoses – US 2014: 45,220

• 9\textsuperscript{th}–10\textsuperscript{th} most common cancer

• 3\% of all new cancers

• Overall 5-year survival low and stable


Projected Burden of Cancer

Development of Pancreas Ca


Genetic Evolution of Pancreas Ca

Pancreatic Ductal Adenocarcinoma

A Formidable Tumor Biology...

• Complex microenvironment
• Physical barrier to effective drug delivery (stroma)
• Relative immune suppression
• Multiple gene mutations
• Key genes can’t be targeted
Localized Pancreas Cancer

3 Key groups:

- Localized, operable (stage I-IIB)
- Localized, 'borderline' operable
- Locally advanced, non-operable (stage III)

Clinical Features & Presentation

- Common symptoms: weight loss, appetite loss, jaundice, pain, malabsorption, new diabetes

- Symptoms depend on primary tumor location
  - Head tumors: weight loss, jaundice
  - Body/ tail tumors: weight loss, back/flank pain

- Blood clots: DVT or PE, presenting symptom in advanced disease (Trousseau)
Surgical Considerations

• Absence of spread of cancer

• Key issue is the relationship of primary tumor to blood vessels
  – CT pancreas angiography – most useful

• Confirmed diagnosis of malignancy not necessitated in right clinical setting

• Laparoscopy – used selectively

Operable Pancreas Cancer
Surgery for Pancreas Adenocarcinoma

- Pancreatectoduodenectomy (Whipple) 80%
- Distal Pancreatectomy +/- Splenectomy 20%

Adjuvant (Postoperative) Therapy

- Gemcitabine or 5-fluorouracil (5-FU) for 6 months
- Data for inclusion of combined chemotherapy and radiation – more controversial
  - US – often included
  - Europe, Japan – typically chemotherapy alone
  - Large study underway to define absolute benefit of chemotherapy + radiation (RTOG 0848)
- Other trials evaluating adding agent to gemcitabine
Why Neoadjuvant (Pre-operative) Therapy?

• Risk of recurrence
• Selects out cancer behaviour, avoidance of surgery
• Improved treatment delivery: 20-25% don’t receive adjuvant therapy in view of post-op issues
• Improved margin negative operations, reduced local recurrence rate, ‘downstaging’?
• Standard approach in other GI cancers

CT Pancreas Scan: Borderline Resectable
Hypovascular pancreas head tumor
Inoperable Pancreas Cancer

Head of Pancreas & Liver Metastases
Multidisciplinary Management

- Pain management
  - Narcotics, nerve block
  - Supportive/ palliative care
- Jaundice
  - ERCP + bile duct stent, operative bypass
- Duodenal (gastric outlet) blockage
  - Stent, drainage tube (dPEG), rarely surgery
- Nutrition
  - Enzyme supplementation, appetite enhancement
- Blood clots > 30-50%
- Psychosocial care

‘Approved’ Treatments For PC

- Gemcitabine
- Erlotinib
- Nab-paclitaxel
- FOLFIRINOX
- S1*

*Approved only in Japan
Goals of Treatment

- Control the cancer
- Ease symptoms
- Extend life
- Maintain/improve quality of life

FDA Approval 1996
Gemcitabine vs 5-FU Phase III Trial

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N= 63</td>
<td>N= 63</td>
</tr>
<tr>
<td>Clinical Benefit Response</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>1-year Survival</td>
<td>18%</td>
<td>2%</td>
</tr>
</tbody>
</table>

FOLFIRINOX vs Gemcitabine
Prodige 4- ACCORD 11

Untreated Metastatic Panc Adenocarcinoma ECOG 0-1

Randomize

FOLFIRINOX N= 167

Gemcitabine N= 169

Primary Endpoint: Overall Survival


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FOLFIRINOX vs Gemcitabine
Overall Survival

- Median 11.1 mths for FOLFIRINOX
- Median 6.8 mths for Gemcitabine

HR = 0.57
P < 0.0001

Conroy, T. NEJM, 2011
## FOLFIRINOX vs Gemcitabine

### Other Trial Endpoints

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX N= 167</th>
<th>Gemcitabine N= 169</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low white cells + fever</td>
<td>5 %</td>
<td>0.6%</td>
</tr>
<tr>
<td>Low platelets</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Nerve effects</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>White cell booster needed</td>
<td>43%</td>
<td>5%</td>
</tr>
<tr>
<td>Tumor Shrinkage</td>
<td>32%</td>
<td>9%</td>
</tr>
<tr>
<td>Cessation tumor growth</td>
<td>6.4 m</td>
<td>3.3 m</td>
</tr>
</tbody>
</table>


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### FOLFIRINOX Delays Worsening Quality of Life

![Graph showing FOLFIRINOX Delays Worsening Quality of Life](image)

Metastatic Pancreas Adenoca Trial (MPACT)

Primary Endpoint: Overall Survival

Nab-Paclitaxel + Gemcitabine N= 431
Gemcitabine N= 430

MPACT Trial: Outcome

OS, months

<table>
<thead>
<tr>
<th></th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem</td>
<td>8.5 (7.89-9.53)</td>
</tr>
<tr>
<td>Nab-P + Gem</td>
<td>6.7 (6.01-7.23)</td>
</tr>
</tbody>
</table>

HR = 0.72
P = .000015

Which Treatment First For PC?

• No clear data to guide
  - Age, level of well-being, patient preference
• Nab-paclitaxel and gemcitabine – applicable to broader patient population
  - Older, less robust
  - Easier to add other agents?
• Ability to select which regimen first will be useful

Second-Line Therapy in Pancreatic Adenocarcinoma

• No standard/approved therapy for second line (yet…)
• Data to support gemcitabine-based treatment for patients with disease growth on 5-FU-based regimen
• Data to support 5-FU-based therapy for patients with disease growth on gemcitabine-based therapy
• Relatively few patients enrolled on trials in a second-line setting
Targeting Inflammation in PC
RECAP Trial

- Randomized phase II capecitabine ± ruxolitinib
- N= 138 with progressive met PDAC following prior gemcitabine-based therapy
- Primary endpoint: Survival

- **Subgroup:** 50% with elevated C-reactive protein (CRP)
  - Improvement in outcome with addition of ruxolitinib

ASCO, 2014

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MM-398: New Chemotherapy

- Irinotecan – encapsulated for improved delivery/efficacy (lipid nanoparticle)
Randomized Phase III Trial
Previously Treated Pancreas Cancer

Previously Treated Pancreas Adenocarcinoma N= 417

Combination of MM-398 + 5-FU/LV – most beneficial
Under FDA review – 2015?

Where Do We Go From Here?

• Interfering with the stroma
• Targeted therapy for genetic subgroups
• Targeting cancer stem cells
• Immune therapies
• Specific inhibitors of key signaling pathways
• New chemotherapy (cytotoxic) agents
Clinical Trials

- **Phase I**
  - Dosing, schedule, side effects, hints of efficacy

- **Phase II**
  - Typically restricted to a specific disease
  - Estimation of the effectiveness of the therapy
  - Fuller understanding of side effects

- **Phase III**
  - Comparison to best standard treatment
  - Gold standard approach for drug approval

- **Phase IV**
  - Post FDA drug approval assessment

Clinical Trials II

- **Support for clinical trials**
  - Government (NCI)
  - Pharmaceutical industry
  - Philanthropy,
  - Academic Institutions

- **Regulatory control/ support for clinical trials**
  - Institutional Review/ Privacy Board
  - Large trials – Data & Safety monitoring committee
  - Principal investigator - responsibility
Types of Clinical Trials

• Therapeutic
  – Treat the cancer
  – Treat the symptoms

• Non-therapeutic
  – Data collection
  – Investigate biology, outcomes in subgroups

Considering a Clinical Trial

• Things to think about...
  – Goal of study and your goals
  – State-of-the-art care
  – Better than state-of-the-art?
  – Advancing knowledge

• Appropriate for your setting?
  – Mostly for patients without prior treatment
  – Adequate general health (aside from cancer)
Pancreatic Cancer Trial Accrual 2011
(Courtesy Pancreatic Cancer Action Network)

<table>
<thead>
<tr>
<th>Target/Frequency</th>
<th>Class of Drug</th>
<th>Example of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS (90%), RAK, MEK</td>
<td>FT inhibitor; Oncolytic virus C-Met</td>
<td>Tipifarnib, Salarasib; Reovirus, Selumetinib, Onartuzumab</td>
</tr>
<tr>
<td>EGFR (40-70%)</td>
<td>TKI's, monoclonal Antibodies</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>mTOR/ P13K/ AKT/ MEK</td>
<td>mTOR inhibitor AKT, P13K, MEK</td>
<td>Everolimus, temsirolimus MK-2206, XL-765, BKM-120, Selumetinib</td>
</tr>
<tr>
<td>Hedgehog (70%) Notch (60-70%)</td>
<td>Small molecule Shh inhibitor Gamma-secretase inhibitor</td>
<td>GDC-0449, IPI-926, LDE-225 R04929097, OMP-59R5</td>
</tr>
<tr>
<td>PSCA</td>
<td>Antibody to PSCA</td>
<td>AGS-1C4D4</td>
</tr>
<tr>
<td>SRC</td>
<td>SRC, bcr-abl inhibitor</td>
<td>Dasatinib, AZD 0530</td>
</tr>
<tr>
<td>PARP/BRCA/PALB2</td>
<td>PARP inhibitors</td>
<td>AZD 2281, Veliparib, BSI-201</td>
</tr>
<tr>
<td>Vaccines/Immune</td>
<td>CTLA4, PD-1, PD-L1, CD40 CAR mesothelin</td>
<td>Ipilimumab, Nivolumab, CRS-207, GVAX, Algenpantucel-L</td>
</tr>
</tbody>
</table>

New Targets, New Drugs...

Targeting the Tumor Microenvironment

Hyaluronan in the Stroma as a Target in Pancreatic Cancer

- Hyaluronan increased in >80% of pancreatic cancers
- Tumors that accumulate hyaluronan develop high pressure and drug resistance
- Hyaluronan is associated with disease progression and poor prognosis

Nab-Paclitaxel + Gemcitabine +/- PEGPH20
Randomized Phase II Trial

Primary Endpoint: Disease control

http://clinicaltrials.gov/show/NCT01839487

Pancreatic Cancer, BRCA, and PARP Inhibition

- 5%-10% of pancreatic cancer patients have inherited BRCA-1 or -2 gene mutation
  - Ashkenazi Jewish, Scandinavian, Icelandic, others

- BRCA-1, -2 involved in DNA repair

- PARP inhibition established value in ovarian/breast cancer with BRCA-related mutations

- Emerging data in pancreatic cancer supports targeting genetic vulnerabilities related to BRCA gene mutations
Randomized Phase II Trial in BRCA-Mutated Pancreas Adenoca

Pancreas cancer with BRCA1-2, PALB2 mutation

Arm A: Cisplatin + gemcitabine + veliparib
Arm B: Cisplatin + gemcitabine

Gemcitabine + cisplatin d3+10, q21
Veliparib dosing, day 1-12 twice daily by mouth


Pancreas Cancer BRCA Mutation

Ca 19-9 2660; CEA 229
Ca 19-9 42; CEA 4.3
Immunotherapy Trials in PC

- Algenpantucel-L (NewLink Genetics): human PC cell lines genetically engineered to express αGal
  - Completed study in surgically removed pancreas cancer
- Nivolumab (PD1) ± ipilimumab (anti-CTLA4)
- MEDI4736 (PDL1)
- Engineered T-cells (CAR)
  - Mesothelin, CEA
- Clivatuzumab – mAb hPAM40 + ⁹⁰Y (radioimmunotherapy)

ECLIPSE Trial
Randomized Phase IIB

*Previously Treated Metastatic Panc Adenocarcinoma N= 240

- Cyclophosphamide + GVAX + CRS 207
- CRS 207
- Chemotherapy*

*Gemcitabine/ Capecitabine/ Erlotinib/ Irinotecan
Primary Endpoint: Overall Survival

NCT02004262
Front-Line Metastatic Trials
Selected Randomized Phase II

<table>
<thead>
<tr>
<th>NCT</th>
<th>Trial Design</th>
<th>N</th>
<th>Target</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>01839487</td>
<td>Gem + nab-paclitaxel ± PEGPH20</td>
<td>132</td>
<td>Hyaluronan</td>
<td>Halozyme</td>
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<tr>
<td>01621243</td>
<td>Gem + nab-paclitaxel ± M402</td>
<td>148</td>
<td>Anti-stromal</td>
<td>Momenta</td>
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<tr>
<td>01647828</td>
<td>Gem + nab-paclitaxel ± OMP-59R5</td>
<td>140</td>
<td>Notch, stem cell</td>
<td>OncoMed</td>
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<tr>
<td>01844817</td>
<td>Gem + nab-paclitaxel ± OGX-427</td>
<td>132</td>
<td>HSP27</td>
<td>OncoGenix</td>
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<tr>
<td>01016483</td>
<td>Gem ± MSC1936369B</td>
<td>174</td>
<td>MEK</td>
<td>Merck, EU</td>
</tr>
<tr>
<td>01728818</td>
<td>Gem ± afatinib</td>
<td>117</td>
<td>EGFR, HER2,4</td>
<td>Boehringer, EU</td>
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<tr>
<td>01509911</td>
<td>Gem ± TL-118</td>
<td>80</td>
<td>Angiogenesis</td>
<td>Tilman Pharma</td>
</tr>
<tr>
<td>01505530</td>
<td>LY2495555 + chemo (invest choice)</td>
<td>120</td>
<td>Myostatin</td>
<td>Eli-Lilly</td>
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<tr>
<td>01280058</td>
<td>Carbo + paclitaxel ± reovirus</td>
<td>70</td>
<td>RAS</td>
<td>NCI</td>
</tr>
<tr>
<td>01585805</td>
<td>Gem + cisplatin ± veliparib</td>
<td>~70</td>
<td>PARPi (BRCA+)</td>
<td>NCI, Lustgarten</td>
</tr>
<tr>
<td>01209111</td>
<td>Gem + erlotinib ± metformin</td>
<td>120</td>
<td>Multiple</td>
<td>U. Amsterdam</td>
</tr>
<tr>
<td>01167738</td>
<td>PEXG ± metformin</td>
<td>82</td>
<td>Stem cells</td>
<td>San Raffaele</td>
</tr>
</tbody>
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Conclusions

1. Treatment works in PC
2. Adjuvant therapy: Gemcitabine +/- chemoradiation
3. For high functioning individuals with metastatic disease
   Multi-drug combination, e.g.,
   FOLFIRINOX,
   Gemcitabine + nab-paclitaxel
4. For all – clinical trials where possible
5. Multiple interesting agents in development
Conclusions II

• Second-/third-line therapy trials feasible and area for drug development

• Ongoing needs
  • Validated markers for patient treatment selection
  • Enhanced clinical trial participation

• Future looks brighter...

Expectations For The Future

1) Improved understanding of who is at risk
2) Increased role of screening for PC
3) Improved model systems of PC
4) Improvements in treatment
5) Improvements in molecular classification