PANCREATIC CANCER TREATMENT APPROACHES

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Emory University

Not all cancers arising in the pancreas are the same
Cancers of the Pancreas

- Pancreas has several different functions.
  - Digestive function - carried out by exocrine gland
  - Hormone production - endocrine gland
- Cancer can arise from either of these parts
  - Cancer from the exocrine gland - “Common” pancreas cancer known as adenocarcinoma
  - Cancer from endocrine gland is called carcinoid or neuroendocrine tumor accounts for 5%
  - Other rare tumors: acinar, lymphoma

Risk Factors
Pancreatic Cancer - Risk Factors

- Cigarette smoking
- Possible relation to diabetes
- Chronic Pancreatitis
- Familial syndromes:
  - Familial Atypical Multiple Mole Melanoma (p16)
  - HNPCC
  - BRCA2
  - Peutz-Jeghers
  - Ataxia-telangiectasia

How does pancreas cancer start?
Global genetic analysis of core signaling pathways in pancreas cancer

- 24 tumors
- 35 authors
- 20,661 genes
- Average 63 alterations per patient
- Mostly point mutations
Presentation

• 70% are in the head of pancreas
• Clinical Presentation:
  – Jaundice
  – Pain: back pain or midepigastic pain
  – Constitutional Symptoms: weight loss, fatigue
  – New onset diabetes: present 10% of cases
  – Other: Pancreatitis, GI bleed, obstruction

Treatment of Pancreas Cancer
Staging

• Early stage- resectable disease
• Borderline resectable
• Locally advanced unresectable
• Late stage (Metastatic) advanced disease-
Cancer has spread to other organs

Treatment

- Surgery
- Radiation Therapy
- Systemic therapy
What is resectable disease?

1. Removal of all the cancer (complete resection) is necessary for long-term survival and for benefit from surgery.
2. Margin-negative resection rates fall with major vessel involvement, while complication rates rise.
3. Major vessel resection (other than SMA) maybe associated with acceptable survival.
4. “Down-staging” of locally advanced PC may improve margin-negative resection rates.

Resectable
Locally Advanced

Borderline resectable
Localized Pancreatic Cancer
Three unique clinical entity

<table>
<thead>
<tr>
<th>Substage</th>
<th>Therapeutic Goal</th>
<th>Surgery</th>
<th>Preoperative Tx</th>
<th>Vascular Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>Cure</td>
<td>Probable</td>
<td>Optional</td>
<td>Unlikely *</td>
</tr>
<tr>
<td>Borderline</td>
<td>Cure</td>
<td>Possible</td>
<td>Preferred *</td>
<td>Likely</td>
</tr>
<tr>
<td>Unresectable</td>
<td>Palliation</td>
<td>Improbable</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Group

- Volkan Adsay
- Field Willingham
- Steven Keilin
- Qiang Cai
- Ken Cardona
- Charles Staley
- David Kooby
- Shishir Maithel
- Bassel El-Rayes
- Walid Shaib
- Jerome Landry

Team

- Tumor Board
- GI Working Group
Survival after Pancreatico-duodenectomy

<table>
<thead>
<tr>
<th>Path status</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 405)</td>
<td>18%</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>14%</td>
</tr>
<tr>
<td>Lymph node negative</td>
<td>32%</td>
</tr>
<tr>
<td>Lymph node negative &amp; negative margins (n = 64)</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Resectable Disease**

- Several trials have shown that the addition of chemotherapy (gemcitabine or 5FU) after surgery improves patient outcomes.
- Role of radiation is still controversial with studies showing mixed results.
- Role of more aggressive chemotherapy regimens using combination of drugs or immune therapy agents are in progress.

**Future Directions - RTOG 0848**

5 cycles

1 cycle

- Gemcitabine
- Gemcitabine
- FP/XRT

Surgical and Radiotherapy Quality Assurance Reviews
Borderline resectable disease

- There is agreement that this group should receive therapy prior to resection.
- Therapy can consist of
  - Chemotherapy (usually combination)
  - Chemotherapy and radiation
  - Chemotherapy followed by chemotherapy and radiation
Emory preoperative therapy trial

- Phase 1 with SBRT dose escalation to the retroperitoneal margin only
- 10 patients accrued
- 9 completed chemoRT
- Promising strategy

FOLFORINOX
Three Cycles

SBRT
3 Days

Surgery

MRI
Tissue

MRI
Tissue
Alliance A021101
(NCT01821612)

- Alliance for Clinical Trials in Oncology
  - SWOG, ECOG, RTOG
  - Multi-institutional treatment trial for patients with BRPC

FOLFIRINOX ➞ CAPECITABINE ➞ SURGERY ➞ GEM

EBRT (50.4)

Locally Advanced Disease
Treatment options

• There is currently no one way to treat this stage
• Most commonly treatment would include
  – Chemotherapy for 4 to 6 months
  – Chemoradiotherapy
• Role of radiation and role of combination chemotherapy in this group is evolving and clinical trials are ongoing to identify the best sequence.

Metastatic Disease
Treatment Metastatic disease

- Therapy for metastatic disease is mainly chemotherapy.
- There are a number of therapeutic options currently available ranging from single agent (gemcitabine) to combinations (gemcitabine nab paclitaxel OR FOLFIRINOX)

Prodige 4 - ACCORD 11 trial design

- **Metastatic pancreatic cancer**
- **Folfirinox**
- **Gemcitabine**

**Stratification**: center, performance status: 0 versus 1, location of the tumor: head versus other location of the primary

**for both arms**: CT scans: obtained every 2 months, 6 months of chemotherapy recommended
### Objective response rate

<table>
<thead>
<tr>
<th></th>
<th>Folfirinox (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>31%</td>
<td>9.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR/PR 95% CI</td>
<td>[24.7-39.1]</td>
<td>[5.9-15.4]</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.6%</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>Disease control CR+PR+SD</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Progression</td>
<td>15.2%</td>
<td>34.5%</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>14.6%</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Median duration of response</td>
<td>5.9 mo.</td>
<td>4 mo.</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Progression free survival

**Median PFS Folfirinox: 6.4 mo.**  **Median PFS Gemcitabine: 3.3 mo**

![Graph showing progression free survival](image)
**Overall Survival**

![Overall Survival Graph]

- **HR**: 0.57
- **95% CI**: [0.45-0.73]
- **Stratified Log-rank test, p<0.0001**

**Number at risk**
- Gemcitabine: 171134, 89, 48, 28, 14, 7, 6, 3, 2, 2, 2
- Folfirinox: 171146, 116, 81, 62, 34, 20, 13, 9, 5, 3, 2, 2

**Study Design**

- **Planned N = 842**
  - Stage IV
  - No prior treatment for metastatic disease
  - KPS ≥ 70
  - Measurable disease
  - Total bilirubin ≤ ULN
  - No age limitation

- **Primary endpoint**
  - OS

- **Secondary endpoints**
  - PFS and ORR by independent review (RECIST)

- **Safety and tolerability**
  - By NCI CTCAE v3.0

**nab-P**
- 125 mg/m² IV qw 3/4
- + Gem 1000 mg/m² IV qw 3/4

**Gem**
- 1000 mg/m² IV qw 7/8 then qw 3/4

1:1, stratified by KPS, region, liver metastasis

Von Hoff et al. ASCO 2013.
**Overall Survival**

<table>
<thead>
<tr>
<th>OS, months</th>
<th>Events/n (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nab-P + Gem</td>
<td>333/431 (77)</td>
<td>8.5 (7.89-9.53)</td>
<td>14.8</td>
</tr>
<tr>
<td>Gem</td>
<td>359/430 (83)</td>
<td>6.7 (6.01-7.23)</td>
<td>11.4</td>
</tr>
</tbody>
</table>

HR = 0.72
95% CI (0.617-0.835)
P = 0.000015

**PFS by Independent Review**

<table>
<thead>
<tr>
<th>PFS, months</th>
<th>Events/n (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nab-P + Gem</td>
<td>277/431 (64)</td>
<td>5.5 (4.47-5.95)</td>
<td>9.2</td>
</tr>
<tr>
<td>Gem</td>
<td>265/430 (62)</td>
<td>3.7 (3.61-4.04)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

HR = 0.69
95% CI (0.581-0.821)
P = 0.000024

PFS Rate at
- 6 months: Nab-P + Gem 44%, Gem 25%, Increase 76%
- 12 months: Nab-P + Gem 16%, Gem 9%, Increase 78%
### Response Rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>nab-P + Gem (n = 431)</th>
<th>Gem (n = 430)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent review, % (95% CI)</td>
<td>23 (19.1-27.2)</td>
<td>7 (5.0-10.1)</td>
<td>1.1 x 10^{-10}</td>
</tr>
<tr>
<td>Investigator assessment, % (95% CI)</td>
<td>29 (25.0-33.8)</td>
<td>8 (5.3-10.6)</td>
<td>3.3 x 10^{-16}</td>
</tr>
<tr>
<td>Disease control rate by independent review, % (95% CI)</td>
<td>48 (43.0-52.6)</td>
<td>33 (28.4-37.5)</td>
<td>7.2 x 10^{-6}</td>
</tr>
</tbody>
</table>

* Includes CR + PR + SD ≥ 16 weeks.

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A Phase Ib Clinical Study of BBI608 in Combination with Gemcitabine and nab-Paclitaxel in Adult Patients with Metastatic Pancreatic Adenocarcinoma
Familial Pancreatic Cancer

- **BRCA2** – Pancreas, Ovarian, Breast. Increased sensitivity to PARP inhibitors

- **PALB2** and **BRCA2**- Increased sensitivity to DNA damaging agents such as mitomycin C

- DNA mismatch repair (MMR) genes such as **MLH1, MSH2, MSH3, MSH6, PMS1**, and **PMS2**. Pancreatic tumors with MSI phenotype maybe more sensitive to irinotecan based regimens.

**BRCA Mutations and PARP Inhibitors**

Pre-Treatment  |  Post-Treatment
Promising new drugs

- Immune therapy
  - Checkpoint inhibitors
  - Vaccines
- Signaling pathway
  - JAK-2 inhibitors
- Chemotherapy agents
  - Liposomal irinotecan
Pain Control

- Pain medication
  - Short acting
  - Long acting
- Constipation
  - Prevention
  - Treatment
- Celiac block
Ascites

• Common complication in advanced stage disease

• Management
  – Paracentesis
  – Catheter placement

Resources

• Support groups
• NIH site: www.clinicaltrials.gov
• Patient directed sites:
  – NCI (http://www.cancer.gov)
  – ASCO (http://www.cancer.net)
  – ACS (http://www.cancer.org)
• PanCan (https://www.pancan.org)
Conclusion

• Surgery is still the treatment of choice for resectable disease.
  – Chemotherapy in the adjuvant setting has shown an impact on OS
• Borderline resectable disease treatment is usually pre-operative chemo or chemoradiotherapy followed by resection
• Locally advanced unresectable disease therapy is palliative.
  – Role of radiation is still controversial.
• Metastatic disease treatment is palliative. Options include FOLFIRINOX, gemcitabine and nab-Paclitaxel or gemcitabine single agent
• Treatment plan should include a comprehensive approach to address symptoms as well as the underlying disease.

Thank You