Treatment Approaches for Pancreatic Adenocarcinoma

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Webinar, Pancreatic Cancer Action Network
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**Pancreatic Adenocarcinoma**

- ~ 39,000 patients diagnosed every year in the U.S.
- Systemic disease in most patients; rarely curable
- **100 Patients**
  - 15-20 patients will have operable tumors
  - 80 will have inoperable, advanced cancers
  - 3 - 4% five year survival; in most survival measured in months

**Pancreatic Cancer - Often presents late**

- ‘Nonspecific’ symptoms which can mimic other common conditions
- ‘Tucked away’: no early symptoms
- No good screening test
Staging of Pancreatic Cancer

- **Resectable** (Stages I and II)
  - Stage 1: Isolated in the Pancreas, no lymph nodes or blood vessels involved
  - Stage II: Extends beyond the pancreas. No blood vessels involved

- **Unresectable** (Stages III and IV)
  - Stage III: Blood vessels involved
  - Stage IV: Spread to distant organs
Clinical staging of Pancreatic cancer

I. Resectable (10-15%)

II. Locally advanced (50%)

III. Metastatic (35-40%)

Tools used: Physical examination and blood tests, CT scan, Endoscopic ultrasound, biopsy
Borderline Resectable Pancreatic Cancer

Patterns of Spread

- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Other
### Treatment options for Pancreatic Cancer

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Radiation</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable</strong></td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Borderline</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Resectable</strong></td>
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<tr>
<td><strong>Locally</strong></td>
<td>-</td>
<td>+/-</td>
<td>+</td>
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<tr>
<td><strong>Advanced</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>
Resectable Pancreatic Cancer

SMV

SMA

T

Standard Approach to Resectable (head) Tumors

FACTS

- Pancreaticoduodenectomy
- 15-20% long term survival
- Recurrence rate 80% to 85%
- 20 - 30% patients do not receive post-operative therapy
- Median survival 20-26 months

GITSG 1987, EORTC 1999, ESPAC 2004
Therapy options after surgery

• Chemotherapy
  – To kill any microscopic cancer floating around in the blood and other organs….

• Radiation (Controversial)
  – To prevent tumor from coming back in the surgical bed.

Current Status of Postoperative Adjuvant therapy for Resected Pancreatic Cancer
## Randomized Trials of Adjuvant Therapy

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Number of Patients</th>
<th>Pts with R1 Resection (%)</th>
<th>Treatment</th>
<th>Treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median Survival Months</td>
<td>Median Survival Months</td>
<td></td>
</tr>
<tr>
<td>GITSG (1985)</td>
<td>49</td>
<td>0</td>
<td>5-FU + XRT 21.0</td>
<td>Observation 10.9</td>
<td>0.035</td>
</tr>
<tr>
<td>EORTC 40891 (1999)</td>
<td>114</td>
<td>21</td>
<td>5FU + XRT 17.1</td>
<td>Observation 12.6</td>
<td>0.09</td>
</tr>
<tr>
<td>ESPAC-1 (2004)</td>
<td>289</td>
<td>18</td>
<td>5-FU Chemotherapy 20.1</td>
<td>No Chemotherapy 15.5</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-FU- XRT 15.9</td>
<td>No XRT 17.9</td>
<td>0.05</td>
</tr>
<tr>
<td>RTOG 9704 (2006)</td>
<td>380 (Head lesions)</td>
<td>&gt; 35</td>
<td>GEM then 5-FU/XRT then GEM 20.6</td>
<td>5-FU then 5-FU/XRT then 5-FU 16.9</td>
<td>0.033</td>
</tr>
<tr>
<td>CONKO 001 (2007-08)</td>
<td>368</td>
<td>19</td>
<td>Gemcitabine 22.8</td>
<td>Observation 20.2</td>
<td>0.005</td>
</tr>
<tr>
<td>ESPAC 3 (2009)</td>
<td>1088</td>
<td>35</td>
<td>5FU</td>
<td>Gemcitabine 23.6</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23 months</td>
<td>23.6 months</td>
<td></td>
</tr>
<tr>
<td>CapRI (2010)</td>
<td>110</td>
<td>39</td>
<td>5FU</td>
<td>28.5 months</td>
<td>Not signif</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5FU/XRT(+IF) +XRT (+5FU x 2) 2 months</td>
<td>Not signif</td>
<td></td>
</tr>
</tbody>
</table>

## Role of Post op Chemo alone in Resected PC

Results from CONKO-001 and ESPAC-3

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts</th>
<th>R1 Resection (%)</th>
<th>Treatment</th>
<th>Treatment</th>
<th>P</th>
</tr>
</thead>
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<tr>
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<td>Median Survival Months</td>
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<td></td>
</tr>
<tr>
<td>CONKO 001</td>
<td>368</td>
<td>19</td>
<td>Gemcitabine 22.8 (DFS =13.9)</td>
<td>Observation 20.2 (DFS=6.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>ESPAC 3 (V2)</td>
<td>1088</td>
<td>35</td>
<td>5FU</td>
<td>Gemcitabine 23.6</td>
<td>0.39</td>
</tr>
</tbody>
</table>

1. Gemcitabine stays the reference standard given better tolerability
2. BUT… we do need to figure out which chemo helps whom

CONKO 001 Cetelle H, et al. JAMA, 2007
ESPAC 3 Neoptolemos JP et al. ASCO 2009
Role of Post op Radiation Therapy (RT) for Resected PC

- Current role of RT in the adjuvant setting stays controversial
- Trials evaluating Chemotherapy vs. Chemo-RT (with attention to optimal design and tissue acquisition) need to be encouraged

Adjuvant therapy in Resectable Pancreatic Cancer

- Adjuvant studies suggest that something is better than nothing for patients who have recovered adequately from surgery.
- Not enough progress made in the adjuvant setting over the last 25+ yrs.
  - need to get novel agents in adjuvant setting
  - optimized trial designs
Preoperative vs. Postoperative Approach to Resectable Pancreatic Cancer

Sequencing Therapies for Resectable cancers

- **Traditional approach in patients**
  - Operable Pancreatic Cancer
  - Surgery
  - Post-Operative Therapy (Adjuvant Therapy)

- **Preoperative therapy approach in select patients**
  - Operable Pancreatic Cancer
  - Preoperative Therapy (Neo-adjuvant Therapy)
  - Surgery
Rationale for Pre-Operative Therapy

- Deliver multimodality therapy to all patients with potentially resectable disease
- Provide early treatment of micro metastatic disease
- Avoid surgery in patients with rapidly progressive cancer
- Observe tolerance to therapy to predict tolerance to aggressive surgery
- Potentially improve negative margin resection

Summary of UTMDACC Trials of Pre-Operative Chemoradiation for Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Preoperative therapy</th>
<th>Pts</th>
<th>Wks from Dx to Restaging</th>
<th>Resection rate</th>
<th>Path PR</th>
<th>Survival Resected Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU+RT (50.4 Gy)</td>
<td>28</td>
<td>10-12</td>
<td>61%</td>
<td>41%</td>
<td>18 mo</td>
</tr>
<tr>
<td>5FU+RT (30 Gy)</td>
<td>37</td>
<td>6-8</td>
<td>57%</td>
<td>20%</td>
<td>25 mo</td>
</tr>
<tr>
<td>Paclitaxel +RT (30 Gy)</td>
<td>35</td>
<td>6-8</td>
<td>57%</td>
<td>21%</td>
<td>19 mo</td>
</tr>
<tr>
<td>Gem + RT (30 Gy)</td>
<td>86</td>
<td>11-12</td>
<td>73%</td>
<td>59%</td>
<td>34 mo</td>
</tr>
<tr>
<td>Gem + Cis x 2 mo followed by Gem + RT (30 Gy)</td>
<td>90</td>
<td>17-18</td>
<td>66%</td>
<td>61%</td>
<td>31 mo</td>
</tr>
</tbody>
</table>
Preoperative Program at M.D. Anderson

- Average time between start of preoperative therapy and surgery is about 3 - 4 months.
- Isolated local progression during therapy is rare.
- Patients deemed unresectable after preoperative therapy are those with distant metastasis seen on restaging scans or at the time of surgery.

Treatment options for Pancreatic Cancer

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<td>+</td>
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<tr>
<td>Metastatic</td>
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<td>-</td>
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Borderline Resectable Pancreatic Cancer

Tumor

Positive Surgical Margin

Treatment Schema—Borderline Resectable

Staging CT

Systemic Therapy

Gemcitabine-based 2-4 months

(Interval CT scan)

Restaging CT

No Progression

Regression

4 to 6 Weeks Break

Treatment Schema

Restaging CT

No Progression

Regression

Surgery

*Consider adjuvant therapy based on duration of preoperative treatment and pathology.
Borderline Resectable Pancreatic Cancer

Viable Tumor

Non-viable rim

Negative Surgical Margin!

After Preoperative Chemotherapy and ChemoRT

Borderline resectable pancreatic cancer

52 year old woman, presenting with borderline resectable pancreatic cancer. The hepatic artery is encased by tumor and splenoportal confluence compressed by tumor. After preoperative therapy lasting 6 months, sufficient tumor reduction to justify surgical resection with curative intent. She is without cancer spread, 50+ months.
Locally Advanced Pancreatic Cancer

- Typically, chemotherapy (2-4 cycles) followed by chemoradiation in select patients is the preferred approach. This strategy allows the best candidates to benefit from locoregional therapy.

- Role of radiation in LAPC is being questioned
  - SCALOP trial – Cape + RT > Gem + RT
  - LAP07 trial – role of RT being questioned; best candidates? (need predictive biomarkers)

Patient with Locally Advanced Disease

This patient was treated with systemic therapy for 4 months with minor response in the primary tumor followed by chemoradiation therapy.
Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study

Primary Endpoint: - OS in R2
Secondary Endpts: - Role of erlotinib, tolerance, predictive markers and CTCs

Restaging
Those with controlled disease proceeded to R2 = 296
2 additional months of CT (136)
Gemcitabine + Erlotinib
Cape + Radiation (133)

OS in R2 pts. was 16.5 m [15.5-18.5] and 15.3 m [13.9-17.3] in arms 1 and 2, respectively (HR=1.03 [0.79-1.34], p=0.83).

Administering CRT is not superior to continuing CT in patients with controlled LAPC after 4 months of CT.
**Metastatic Pancreatic Cancer**

- Average of 63 genetic alterations/cancer
- Majority are point mutations
- Core set of 12 cellular processes are altered
- Is there a hierarchy of core signaling pathways?

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**Treatment options for Pancreatic Cancer**

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Patterns of Spread

- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Other

Gemcitabine: Standard of care since 1996
Advanced Pancreatic Cancer

- Pivotal trial compared Gemcitabine to 5-FU

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>RR</th>
<th>OS*</th>
<th>1-yr Survival*</th>
<th>Clinical Benefit Response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>63</td>
<td>0%</td>
<td>4.41 mo</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Gem</td>
<td>63</td>
<td>5.4%</td>
<td>5.65 mo</td>
<td>18%</td>
<td>22%</td>
</tr>
</tbody>
</table>

P=0.0025

Burris et al, JCO 15: 2403-2413, 1997
Gemcitabine and Erlotinib - Overall Survival

GEMCITABINE ± ERLOTINIB
Phase III Study

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + P</td>
<td>5.91 mo</td>
<td>17 %</td>
</tr>
<tr>
<td>Gem + Erlotinib</td>
<td>6.24 mo</td>
<td>23 %</td>
</tr>
</tbody>
</table>


Randomized phase III trial comparing FOLFIRINOX (F) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma: PRODIGE 4/ACCORD 11 trial.

F: O 85 mg/m2 d1 + l 180 mg/m2 d1 + LV 400 mg/m2 d1 followed by 5FU 400 mg/m2 bolus d1 and 2,400 mg/m2 46h continuous infusion biweekly

G: Gemcitabine 1000 mg/m², 30 min IV wkly 7 on 1 off, then 3 on 1 off

R, Ph II
F>G

PS 0-1
Stratified by: PS, Center, Tumor location

Conroy, et al NEJM 2011
Randomized phase III trial comparing FOLFIRINOX versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): PRODIGE 4/ACCORD 11 trial.

<table>
<thead>
<tr>
<th></th>
<th>F Grade ¾ (%)</th>
<th>G Grade ¾ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>15.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24</td>
<td>14.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>47.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5.7</td>
<td>0</td>
</tr>
</tbody>
</table>

T Conroy et al, ASCO 2010
NEJM, May 2011

PRODIGE 4/ACCORD 11 trial – FOLFIRINOX SURVIVAL AND RESPONSE DATA

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX (n=171)</th>
<th>GEM (n=171)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival mo</td>
<td>11.1 mo</td>
<td>6.8 mo</td>
<td>0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression Free Survival mo</td>
<td>6.4 mo</td>
<td>3.3 mo</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Response Rate %</td>
<td>32 %</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Control Rate %</td>
<td>70 %</td>
<td>51 %</td>
<td></td>
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</tbody>
</table>
Randomized Phase III Study of Weekly nab-Paclitaxel plus Gemcitabine vs Gemcitabine Alone in Patients with Metastatic Adenocarcinoma of the Pancreas (MPACT)

**Planned N = 842**
- Stage IV
- Untreated
- KPS ≥70

**Primary Endpoint:**
- OS

**Secondary Endpoints:**
- PFS & ORR by Independent review

**nab-Paclitaxel:** 125 mg/m² IV qw 3/4 weeks +

**Gemcitabine:** 1000 mg/m² IV qw for 7/8 weeks then qw 3/4 weeks

**Gem 1000 mg/m² IV qw for 7/8 wks then qw 3/4 weeks**

**With 608 events, 90% power to detect OS**

HR = 0.769 (2–sided α = 0.049)

- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

**Von Hoff et al., NEJM 2013**

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**nab-Paclitaxel plus Gemcitabine (MPACT)**

**SAFETY**

<table>
<thead>
<tr>
<th></th>
<th>nabP + GEM (n=421)</th>
<th>GEM (n=402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Neutropenia</td>
<td>3 %</td>
<td>1 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 %</td>
<td>7%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17 %</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 %</td>
<td>1 %</td>
</tr>
</tbody>
</table>

44% patients with peripheral neuropathy resumed nab-P after improvement (median to improvement to grade ≤1 = 29 days)

**Von Hoff et al., NEJM**
**nab-Paclitaxel plus Gemcitabine (MPACT)**

**SURVIVAL AND RESPONSE DATA**

<table>
<thead>
<tr>
<th></th>
<th>nabP + GEM (n=431)</th>
<th>GEM (n=430)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival mo</td>
<td>8.5 mo</td>
<td>6.7 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.72</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Progression Free Survival mo</td>
<td>5.5 mo</td>
<td>3.7 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.69</td>
<td>P &lt;0.001</td>
</tr>
<tr>
<td>Response Rate %</td>
<td>23 %</td>
<td>7%</td>
</tr>
<tr>
<td>(independent review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Control Rate %</td>
<td>48 %</td>
<td>33 %</td>
</tr>
<tr>
<td>(independent review)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DCR : Includes CR + PR + SD ≥16 weeks

Von Hoff et al., NEJM

**Clinical trials: Definitions**

- **PHASE I TRIALS:** An experimental drug is tested in a small group of patients
  - with different cancers (20-40 pts.) for the first time to determine safety,
  - identify side effects and to gain some early evidence of effectiveness

- **PHASE II TRIALS:** Experimental drug is given to a larger group of patients
  - Usually with same cancer to determine effectiveness,
  - monitor side effects, compare it to commonly used drugs

- **PHASE III TRIALS:** Experimental treatment given to large groups of patients
  - to confirm effectiveness, compare it to commonly used drugs (standard of care)
  - if positive, may establish change in standard of care
Novel targets and therapies: Pancreatic Cancer

- **Kras**: Kras mutation occurs in 90%+ pancreatic cancers
  - Could provide a rational therapy for pancreatic cancer
  - With the mutation, Ras gene signalling function is unable to be turned "off"
  - A number of drug companies are investigating ways to halt the signalling function of Ras.

- **Immune checkpoint blockade drugs** (these drugs harness patient’s own immune system to treat cancers)
  - antiCTLA4, anti PD-1

- **IGFR**
- **Notch**
- **cMET**
- **AKT and PI3K**
Novel targets and therapies: Pancreatic Cancer

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  - antiCTLA4, anti PD-1

- IGFR
- Notch
- cMET
- AKT and PI3K

Challenge going ahead is how best to combine some of the targeted drugs with minimal toxicity and how to determine which ones are actually going to be beneficial.
It is important to tackle all symptoms – they feed on each other...domino effect

Communication with the health care team is important

- Is it a side effect of treatment or symptom of cancer
- Many supportive care options to improve quality of life

Summary: Pancreatic Cancer

- Pancreatic cancer is a local disease and a systemic disease
- Accurate staging is essential
- Do not make treatment decision in haste (especially surgery)
- The research teams are working toward personalizing therapies and trials to match the patient
  - More options available with approval of new drugs in the last 2 years
- We have a long way to go but we are definitely making progress
Questions?

Thank you for your participation!

Pancreatic Cancer Action Network
www.pancan.org

If you have questions, please contact our Patient and Liaison Services (PALS) program at (877) 272-6226 or e-mail pals@pancan.org.