What’s New in the Treatment of Pancreatic Cancer?

Lots!

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Fox Chase Cancer Center
September 17, 2013

Overview

• Staging and Workup
• Resectable Disease
  – Surgery
  – Adjuvant therapy
• Locally Advanced
  – Borderline resectable
  – Unresectable
• Metastatic Disease
Epidemiology

- ~43,140 new cases
- ~36,800 deaths
- 4th leading cause of cancer death
- Median age = 69 years
- Males 1.5 X risk of females

How do patients usually present?

- Jaundice
  - Obstructive
  - Often relieved with stent placement by GI
- Abdominal/back pain
  - Direct tumor effect
- Weight loss
  - malabsorption
Usual workup

• Ultrasound (often for jaundice)
• CT scan (can help with diagnosis and staging)
• Endoscopic ultrasound
• PET – not usually required
• If clear pancreatic mass and/or metastatic lesions
  – Biopsy
Pathology

- Adenocarcinoma most common

- There are rarer pancreatic tumor types:
  - Islet cell tumors
  - Acinar cell
  - Squamous cell
There can be a lot of scar and a little tumor!

Once we have a diagnosis and stage…

Clinical categories to guide therapy
Pancreatic Cancer

- Locally advanced: 20-25%
- Metastatic: 20-25%
- Resection: 50%

Borderline Resectable → Categorically Unresectable

Practical Categories and Treatment

- Resectable
  - Surgery
- Locally Advanced - borderline resectable
  - Chemo or Chemo/XRT
- Locally advanced unresectable
  - Chemo or chemo/XRT
- Metastatic
  - Chemotherapy
What makes a tumor resectable?

- No metastatic disease
- No significant vessel involvement
- Patient can tolerate a major operation

Surgery for the non-surgeon!
A Particular Challenge in Pancreatic Cancer

It matters where surgery is done!

<table>
<thead>
<tr>
<th>No. Operations</th>
<th>&lt;1/yr</th>
<th>1-2/yr</th>
<th>3-5/yr</th>
<th>6-16/yr</th>
<th>&gt;16</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>1,563</td>
<td>2,757</td>
<td>1,885</td>
<td>2,166</td>
<td>2,159</td>
</tr>
</tbody>
</table>

Birkmeyer, NEJM 2002;346:1128
Postoperative (Adjuvant) Therapy - Rationale

- Many patients are at risk for recurrence
  - Due to microscopic disease
- Chemotherapy has benefit in advanced disease
- Local recurrence may be an issue
  - Role of radiation therapy

GITSG Adjuvant Trial (Kalser et al, Arch Surg 120:899, 1985)

- Randomized 43 patients over 8 years who underwent curative resection (- margins) of adenocarcinoma of pancreas postoperatively to

  - Split course XRT (20 Gy over 2 weeks X 2)
  - 5-FU 500 mg/m² by bolus for 3 days each XRT cycle, then weekly for up to 2 years
  - Observation
### Results

<table>
<thead>
<tr>
<th></th>
<th>Adjuvant Therapy (n=21)</th>
<th>No adjuvant therapy (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (months)</td>
<td>20</td>
<td>11 (p=.03)</td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>42</td>
<td>15 (p=.03)</td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>19</td>
<td>5 (p=.03)</td>
</tr>
</tbody>
</table>

### ESPAC-1

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy N=147</th>
<th>No chemotherapy N=142</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Median survival (m)</td>
<td>20.1</td>
<td>15.5</td>
<td>0.009</td>
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<tr>
<td>2-year survival (%)</td>
<td>40</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>21</td>
<td>8</td>
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## ESPAC-1

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiotherapy N=145</th>
<th>No chemoradiotherapy N=144</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Median survival (m)</td>
<td>15.9</td>
<td>17.9</td>
<td>0.05</td>
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<tr>
<td>2-year survival (%)</td>
<td>29</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

## CONKO-001 Study Design

- **Resected pancreatic cancer**
  - 368 patients
  - Stratification: R; T; N
  - Gemcitabine for 6 months
  - Observation for 6 months
  - Follow up every 8 weeks
RTOG 9704

**ESPAC-3 Study Design**

- Resected pancreatic cancer
- 1,088 patients
- R0 or R1 resection
- Stratification: margin, country

- Gemcitabine for 6 months
- 5-FU/FA for 6 months

Primary endpoint overall survival

**ESPAC-3 Results**

- Overall survival
- Progression-free survival

Log-rank $\chi^2 = 0.74; P = 0.39$

HR, 0.94 (95% CI: 0.81-1.08)

Log-rank $\chi^2 = 0.40; P = 0.33$

HR, 0.96 (95% CI: 0.84-1.10)
Adjuvant Therapy Overview

- Chemotherapy with modest benefit
  - Gemcitabine or 5-FU
- Radiation therapy still debated
  - Often used if local recurrence a concern
- We use these older studies as a building block to incorporate new advances

Ongoing Adjuvant Studies

- US Cooperative Group
  - Radiation therapy or not
- Outside-US Cooperative Group
  - Gemcitabine vs. FOLFIRINOX
    - Taking recent advance from metastatic disease
- Industry
  - HyperAcute® vaccine – NewLink Genetics
Borderline Resectable 
Versus 
Locally Advanced Unresectable

WARNING!
Only surgeons understand this!!

Don’t feel bad if you are confused!

• On a recent pancreas cancer call, half of the two hour time slot was spent by the surgeons debating the definition of borderline resectable.
• Involves analysis of degree of blood vessel involvement
  – Abutting vessels – borderline
  – Encasing vessels – categorically unresectable
Controversy!

The locally advanced debate..
Is radiation therapy helpful?

A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized unresectable pancreatic cancer: E4201

P. J. Loehrer Sr., M. Powell, H. Cardenes, L. Wagner, J. Brell, R. Ramanathan, C. Crane, S. Alberts, A. B. Benson

On behalf of
The Eastern Cooperative Oncology Group
Recent large study- LAP-07

Hammel et al. ASCO, 2013
Recap of Locally Advanced

- Chemotherapy is an important therapy

  Radiation therapy is commonly used
  - For borderline resectable, commonly
  - For categorically unresectable, sometimes

Remember that our treatment of earlier stage disease utilizes only gemcitabine or 5-FU

Let’s move to some advances in metastatic disease
What about metastatic disease?

So how did we get here?

Available Systemic Agents

- Gemcitabine – “old” standard
- Nab-paclitaxel – just approved with gemcitabine
- 5-Fluorouracil (“5-FU”)
- Oxaliplatin
- Irinotecan
- Erlotinib – oral targeted therapy

FOLFIRINOX
The gemcitabine approval study

**Patient Population**
- Adenocarcinoma of pancreas
- No prior chemotherapy
- Measurable or non-measurable disease
- EGFR status not an eligibility criterion

**Stratification**
- Center
- PS (0/1 vs 2)
- Stage of disease

**Study Schema**

<table>
<thead>
<tr>
<th>Survival time (months)</th>
<th>% patients surviving</th>
<th>GEM ( n=53, 12.7% ) censored</th>
<th>5-FU ( n=53, 4.8% ) censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>70</td>
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<tr>
<td>8</td>
<td>60</td>
<td>60</td>
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<td>10</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>12</td>
<td>40</td>
<td>40</td>
<td>40</td>
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<td>14</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Log-Rank Test
\[ p = 0.0025 \]

ASCO, 2010

FOLFIRINOX
Prodige 4 - ACCORD 11 trial design

Metastatic pancreatic cancer

\[ \text{Randomize} \]

\[ \text{Folﬁrinox} \]

\[ \text{Gemcitabine} \]

for both arms:

- CT scans: obtained every 2 months
- 6 months of chemotherapy recommended

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

Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Folﬁrinox</th>
<th>Gemcitabine</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</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>CR+PR+SD</td>
<td></td>
<td></td>
<td></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

Number at risk
Gemcitabine 171 134 89 48 28 14 7 6 3 3 2 2 2
Folfirinox 171 140 116 81 62 34 20 13 9 5 3 2 2

HR = 0.47 : 95% CI [0.37-0.59]  p = 0.0001

Overall Survival

Number at risk
Gemcitabine 171 134 89 48 28 14 7 6 3 3 2 2 2
Folfirinox 171 140 116 81 62 34 20 13 9 5 3 2 2

HR = 0.57 : 95% CI [0.45-0.73]  Stratified Log-rank test, p = 0.0001
**Safety: hematological AEs**

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th>Gemcitabine N=169</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All, Grade 3/4</td>
<td>All, Grade 3/4</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79.9, 45.7</td>
<td>54.8, 18.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>7.2, 5.4</td>
<td>2.4, 0.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Anemia</td>
<td>90.4, 7.8</td>
<td>94.6, 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75.2, 9.1</td>
<td>54.8, 2.4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

42.5% of the pts received G-CSF in the F arm vs 5.3% in the G arm
One toxic death occurred in each arm
AE, adverse event

**FOLFIRINOX conclusions**

- One standard of care for fit patients
- Caution with biliary stents/infection
- FOLFOX/FOLFIRI also reasonable options
Gemcitabine + Nab-paclitaxel

- Phase 1/2 study
- 63 patients
- Weekly gem
- Weekly nab-paclitaxel 100-150 mg/m2
- RPTD – gem 1000, nab, 125
- 26% PR
- Randomized phase 3 ongoing

Von Hoff et al. ASCO, 2009. Abst 4525

Study Design

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

Primary Endpoint:
- OS

Secondary Endpoints:
- PFS and ORR by Independent Review (RECIST)
- Safety and Tolerability by NCI CTCAE v3.0

- nab-Paclitaxel
  - 125 mg/m² IV qw 3/4 weeks
- Gemcitabine
  - 1000 mg/m² IV qw 3/4 weeks

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

- 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., ASCO GI 2013 LBA148
Overall Survival

- **nab-P + Gem**
- **Gem**

**Proportion of Survival**

<table>
<thead>
<tr>
<th>Months</th>
<th>Proportion of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>21</td>
<td>0.3</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>27</td>
<td>0.1</td>
</tr>
<tr>
<td>30</td>
<td>0.1</td>
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<tr>
<td>33</td>
<td>0.1</td>
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<tr>
<td>36</td>
<td>0.1</td>
</tr>
<tr>
<td>39</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Events/N (%) Median (95% CI) 75th Percentile**

<table>
<thead>
<tr>
<th>Group</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**

Pts at Risk

| nab-P + Gem: 431 | 357 | 269 | 169 | 108 | 67 | 40 | 27 | 16 | 9 | 4 | 1 | 1 | 0 |
| Gem: 430         | 340 | 220 | 124 | 69  | 40 | 26 | 15 | 7  | 3 | 1 | 0 | 0 | 0 |

Safety

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>nab-P + Gem (n = 421)</th>
<th>Gem (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt with at least 1 AE Leading to Death, %</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Grade ≥3 Hematologic AE, a %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Pts Who Received Growth Factors, %</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Febrile Neutropenia, b %</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade ≥3 Nonhematologic AE b in &gt;5% Pts, %</td>
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<td></td>
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<tr>
<td>Fatigue</td>
<td>17</td>
<td>7</td>
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<tr>
<td>Peripheral Neuropathy, c</td>
<td>17</td>
<td>&lt;1</td>
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<tr>
<td>Diarrhea</td>
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<td>1</td>
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<tr>
<td>Grade ≥3 Neuropathy</td>
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<td></td>
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<tr>
<td>Time to Onset, median days</td>
<td>140</td>
<td>113</td>
</tr>
<tr>
<td>Time to Improvement by 1 Grade, median days</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Time to Improvement to Grade ≤1, median days</td>
<td>29</td>
<td>--</td>
</tr>
<tr>
<td>Pts Who Resumed nab-P, %</td>
<td>44</td>
<td>--</td>
</tr>
</tbody>
</table>

a Based on lab values; b Based on investigator assessment of treatment-related events; c grouped term

Von Hoff et al., ASCO GI 2013 LBA148 51, 52
Take-homes from firstline metastatic therapy

• For patients with good performance status combination therapy improves outcome
  – FOLFIRINOX
  – Gemcitabine + nab-paclitaxel
• For patients with borderline performance status single agent therapy may be more appropriate
• For patients with compromised performance status chemotherapy may not be an option
• Ultimate goal to incorporate in locally advanced and resectable states

Second-line therapy for metastatic disease
A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO-003 study.

CONKO-003

U. Pelzer

Kubica K1, Steier J1, Schwaner F, Häll G2, Gerner M3, Möller M4,
Hillig A1, Dorken B1, Riess H1, Oettle H1

1Universität medizin Berlin - Charité Centrum für Tumormedizin; Berlin, Germany;
2Outpatient Department Berlin; 3Klinikum Lübeck; 4Klinikum Bielefeld; 5Outpatient Department Dresden; AIC; Deutsche Krebgesellschaft e.V.

CONKO-003 Results - 2nd line OS

Survival from start of sec. line

<table>
<thead>
<tr>
<th>Group</th>
<th>Median</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>OHS</td>
<td>26 weeks</td>
<td>19.56; 32.41</td>
</tr>
<tr>
<td>OS</td>
<td>13 weeks</td>
<td>10.81; 15.69</td>
</tr>
</tbody>
</table>

Log Rank p=0.014
Second-line therapy

- Some data but fewer studies
- In general, we tend to treat with the “other” type of chemotherapy
- If initial FOLFIRINOX …
  - then gem-based
- If initial gem + nab-paclitaxel…
  - then 5-FU-based

So how do we move forward with our new regimens?

1. Incorporate them earlier
   a. Locally advanced
   b. Adjuvant
2. Add promising new drugs
Incorporating earlier…

- Borderline resectable – US coop study
  - FOLFIRINOX then chemoradiotherapy

And earlier!....

- European postoperative study
  - FOLFIRINOX vs. gemcitabine
Considerations for new drugs

- Generally develop in metastatic disease
- Options:
  - Combine with frontline chemotherapy
    - Generally gemcitabine + nab-paclitaxel
  - As single agent in refractory disease

Examples of ongoing and planned frontline studies

- Gemcitabine/nab-paclitaxel plus
  - ODSH – novel anticoagulant
  - JAK1/2 inhibitor
  - Wnt pathway inhibitor
  - WEE1 inhibitor – US coop group
  - And on and on!!!
Third-line studies ongoing or planned

- Y90-hPAM4
  - Radiolabeled antibody

- MM398
  - Liposomal encapsulated irinotecan

Summary

- There is real optimism about the treatment of pancreatic cancer

- We still have a lot of work to do!

- Key themes in research
  - Developing new drugs
  - Incorporating new regimens earlier in the disease
Thank You!

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