Treatment Approaches for Pancreatic Cancer

January 8, 2015

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Pancreatic cancer: A challenging disease

Pancreas cancer:
- Has the lowest survival of any solid tumor
  - Unfortunately, only 6% of all PC patients are cured
- Is rarely diagnosed early, when it might be curable
  - There are no effective screening tests
  - Vague early symptoms mimic other diseases
  - Nearby blood vessels allow it to spread quickly
- Often doesn’t respond to treatment
  - It is resistant to many drugs
  - The dense stroma around the tumor acts as a barrier to protect the cancer cells from chemotherapy
  - We don’t understand its biology well enough to develop more effective drugs
Within this decade, pancreatic cancer is projected to become the 2nd leading cause of cancer death in the US.

Who gets pancreatic cancer?

**Incidence by gender in 2014:**
- 23,530 men
- 22,890 women

**Deaths by gender in 2014:**
- 20,170 men
- 19,420 women

**Age:**
- Most patients are between age 65 and 80 at diagnosis

**Race:**
- In the US, African-Americans are more likely to develop PC than Caucasians
Risk factors

Tobacco smoking
• >30% of PC cases are due to smoking

Pancreatitis (5% of PC cases)
• Familial >> Acquired

Increasing age

Weaker association:
• Post-gastrectomy, post-cholecystectomy
• Diet: high fat intake, high meat intake
• Diabetes
• Industrial carcinogens

Family History (5-10%)

Familial (inherited) syndromes

<table>
<thead>
<tr>
<th>Familial Syndrome</th>
<th>Genetic abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jaegers</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Familial pancreatitis</td>
<td>PRSS1, SPINK1</td>
</tr>
<tr>
<td>FAMM</td>
<td>CDKN2A</td>
</tr>
<tr>
<td>HNPCC</td>
<td>hMLH1, hMSH2</td>
</tr>
<tr>
<td>Hereditary breast-ovarian syndrome</td>
<td>BRCA1, BRCA2, PALB2</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CFTR</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>p53</td>
</tr>
<tr>
<td>Familial pancreatic cancer</td>
<td>unknown</td>
</tr>
</tbody>
</table>
What are the most common symptoms at diagnosis?

- pain
- jaundice
- weight loss
- decreased appetite
- depression
- nausea/vomiting
- blood clots
- itching
- fatigue
- new onset diabetes

If it looks like pancreas cancer on a scan, why is a biopsy required? Because knowing the pathologic type of pancreas cancer determines treatment options.

Exocrine carcinoma
- **Adenocarcinoma**
  - >90% of PC
- Acinar

Pancreatic neuroendocrine carcinoma (PNET): < 5%
- Important to distinguish
- More indolent
Staging pancreas cancer

• The stage of a cancer refers to the extent of the disease at diagnosis
• Stage is one of the most important factors for deciding treatment options and determining a patient’s prognosis
• Stage is determined by CT scan, endoscopic ultrasound, biopsy, and physical examination. Sometimes stage is determined at surgery

What is the TNM staging system?

• TNM staging is a standard way to determine how much a cancer has spread
  The 3 elements are T, N, and M
  • T: Indicates the size of the tumor in the pancreas and whether it has grown into nearby organs
  • N: Indicates spread to lymph nodes
  • M: Indicates spread to other organs
    – the most common sites of spread are the liver, lungs, or abdominal cavity (peritoneum)
### TNM staging for pancreatic cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>$T_1N_0M_0$</td>
<td>Tumor $\leq$ 2 cm (T1), confined to pancreas. No spread to lymph nodes (N0). No distant spread (M0).</td>
</tr>
<tr>
<td>IB</td>
<td>$T_2N_0M_0$</td>
<td>Tumor &gt;2 cm (T2), confined to pancreas. No spread to lymph nodes (N0). No distant spread (M0).</td>
</tr>
<tr>
<td>IIA</td>
<td>$T_3N_0M_0$</td>
<td>Tumor extends outside pancreas (to bile duct, duodenum, peri-pancreatic tissues) but not into major blood vessels (T3). No spread to lymph nodes (N0). No distant spread (M0).</td>
</tr>
<tr>
<td>IIB</td>
<td>$T_{3-5}N_0M_0$</td>
<td>Tumor has spread to lymph nodes (N1). No distant spread (M0).</td>
</tr>
<tr>
<td>III</td>
<td>$T_{4N_Any}M_0$</td>
<td>Tumor is growing outside the pancreas into nearby major blood vessels or nerves (T4). Lymph nodes may be involved (Any N). No distant spread (M0).</td>
</tr>
<tr>
<td>IV</td>
<td>$T_{Any}N_{Any}M_1$</td>
<td>Distant spread (M1).</td>
</tr>
</tbody>
</table>

### Real world staging and treatment options

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resectable</td>
<td>Can be removed with surgery</td>
<td>Surgery, followed by chemotherapy</td>
</tr>
<tr>
<td>Borderline resectable</td>
<td>Partly wrapped around blood vessels. Might be removable after chemotherapy and radiation</td>
<td>Chemotherapy + radiation, followed by surgery, if possible</td>
</tr>
<tr>
<td><strong>Unresectable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>Cannot be removed. Has not spread</td>
<td>Chemotherapy +/- radiation</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Has spread to other organs</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>
Resectable PC

No distant spread, does not wrap around key blood vessels

Standard treatment for resectable pancreas cancer

Radical pancreaticoduodenectomy (Whipple)
- Removes: proximal pancreas, lower stomach, bile duct, duodenum, proximal jejunum

Other surgical options:
- Head: Whipple with pylorus-preserving procedure
- Body/tail: distal or total pancreatectomy

<15% of PC patients are resectable:
- Operative mortality 1-5%, major morbidity 20%
- Goals is to remove all of the cancer (R0/R1 resection); if you can't remove it all, you don't operate

Post-operative (adjuvant) treatment:
- 6 months of chemotherapy (Gemcitabine or 5-FU)
- Radiation is sometimes given (controversial)
Pancreatico-duodenectomy
“Whipple procedure”

The surgeon really matters

High volume institutions with high volume surgeons have:
- Longer survival
- Fewer surgical complications (morbidity) and fewer deaths (mortality)

• Perioperative mortality:
  - Low volume MD, low volume hospital: ~15%
  - High volume MD, high volume hospital: <3%
Tumor partially encases the SMA, an important blood vessel

Borderline resectable PC

- When the cancer is partly wrapped around a key blood vessel, complete resection is unlikely
- Neo-adjuvant (pre-operative) chemotherapy and radiation is usually given to maximize the chance of completely removing the cancer
- Using the new, more active chemotherapy regimens, FOLFIRINOX and gemcitabine-nab-paclitaxel, may improve the chance of resection

What we still don’t know:
- The best chemotherapy regimen for borderline PC, or how long to give it
- The role of radiation
Unfortunately, about 80% of pancreatic cancers come back after surgery.

The goal of post-operative (adjuvant) chemotherapy:
- To prevent the cancer from coming back
- Or to at least delay it from coming back

Once it returns, it is generally no longer considered curable.
Patterns of recurrence after resection

Poor prognostic factors that suggest that a cancer is more likely to recur after surgery

- Large tumor size (high T stage)
- Poorly differentiated tumors
- + Lymph node involvement
- Positive resection margins (?)
- CA 19-9:
  - High pre-operative level (>1,000)
  - High post-operative level (>180)
  - No decrease after surgery
We give 6 months of gemcitabine after surgery because of the results from the CONKO-001 randomized trial.

CONKO-001: Disease-free survival

Observation: 6.9 mo
Gemcitabine: 13.4 mo
Log rank $P < .001$

Oettle H et al. JAMA. 2007;297:311-313
CONKO-001: Conclusions

- Adjuvant gemcitabine significantly improves both disease-free and overall survival compared to observation.
- Adjuvant gemcitabine is associated with more than twice the rate of 5-year survival.
- The overall survival benefit from gemcitabine holds for R0 and R1 resections, node +/- disease, and all T stages.
- This study supports adjuvant gemcitabine as a community standard.
  - Best level 1 evidence: disease-free survival, median and 5 year survival all superior to observation.
Ongoing clinical trials address unanswered questions regarding adjuvant chemotherapy and radiation for resectable PC

**Radiation**
- Is it beneficial? Is it necessary?

**Chemotherapy**
- Are the newer regimens for advanced disease also better in the post-operative (adjuvant) setting?

**Timing**
- Is it better to give chemotherapy before surgery?

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**Evaluating the role of radiation after surgery: RTOG 0848**

- **Randomize**
  - Gemcitabine x 5 cycles
  - Gemcitabine x 1 cycle
  - Gemcitabine x 1 cycle
  - Radiation + Capecitabine or 5-FU
Incorporating the newer regimens into post-surgical therapy: Phase III trial of adjuvant gemcitabine + nab-paclitaxel

Surgical resection

Randomize

Gemcitabine

Nab-Paclitaxel

Incorporating the newer regimens into post-surgical therapy: Phase III trial of adjuvant FOLFIRINOX vs. Gemcitabine

Surgical resection

Randomize

Gemcitabine

FOLFIRINOX
Evaluating the role of chemotherapy before and after surgery: FOLFIRINOX

FOLFIRINOX x 4 cycles  Surgery  FOLFIRINOX x 4 cycles

Summary: Adjuvant therapy for pancreatic cancer

- Adjuvant therapy options increasingly include systemic chemotherapy alone
- Some data supports 5-FU/LV (ESPAC-1, 3)
- Level 1 evidence supports adjuvant gemcitabine (CONKO-001), which improves disease-free and overall survival
- Relative contribution of chemotherapy vs. chemo-radiation unanswered
- The role of newer regimens (FOLFIRINOX, gemcitabine-nab-paclitaxel) is unknown
Locally advanced PC (LAPC)
A distinct clinical entity

- Disease has not spread, but cannot be removed, usually due to involvement of blood vessels
  - ~1/3 of PC patients
- Different biology, outcomes than metastatic PC

- Role of radiation is controversial
  - Controls pain well
  - Can be difficult to tolerate:
    - Side effects include nausea, vomiting, fatigue
  - Recent LAP-07 trial suggests that radiation may not improve survival
  - Optimal timing of radiation also uncertain

Induction chemotherapy before radiation in LAPC

- Up to 1/3 of LAPC patients develop metastatic disease within the first few months of starting chemotherapy

- Up-front chemotherapy
  - May eradicate occult micro-metastatic disease
  - Spares patients who develop early metastatic progression from toxicities of radiation
  - Limits radiation to patients whose tumors are well-controlled with systemic therapy
GERCOR retrospective analysis in LAPC
Impact of CRT after disease control with chemotherapy

- 181 LAPC pts: chemotherapy for at least 3 months
  - 29% developed metastatic disease during induction chemotherapy
- Investigators choice in the remaining 128 patients
  - Chemo-RT or continue chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Chemo-RT (55%)</th>
<th>Chemo (44%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>10.8 mo</td>
<td>7.4 mo</td>
<td>.005</td>
</tr>
<tr>
<td>OS</td>
<td>15 mo</td>
<td>11.7 mo</td>
<td>.0009</td>
</tr>
</tbody>
</table>

Retrospective study: No definitive conclusions
Hypothesis generating

Huguet, JCO 2007

LAP-07 Trial design
Does CRT ↑ OS in pts w/tumor control after induction chemo?

1st Randomization
- Gemcitabine x 4 months
- Gemcitabine + Erlotinib x 4 months

2nd Randomization
- Gemcitabine x 2 months
- 5040 cGy RT + Capecitabine
- Gemcitabine + Erlotinib x 2 months
- 5040 cGy RT + Capecitabine
- Maintenance Erlotinib
- Maintenance Erlotinib
- Stop
- Stop

Futility boundary for 1st hypothesis crossed after 442 pts randomized

Hammel, ASCO 2013
LAP-07 Results

<table>
<thead>
<tr>
<th></th>
<th>R1+ R2</th>
<th>Gem-chemo</th>
<th>Gem-CRT</th>
<th>GE-chemo</th>
<th>GE-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>68</td>
<td>67</td>
<td>68</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>18 mo</td>
<td>16.7 mo</td>
<td>14.5 mo</td>
<td>14.7 mo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>Gem</th>
<th>Gem-Erlotinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>223</td>
<td>219</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>13.6 mo</td>
<td>11.9 mo</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>10.7 mo</td>
<td>9.3 mo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>R2</th>
<th>Chemo</th>
<th>Chemo-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>136</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>16.4 mo</td>
<td>15.2 mo</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>11.8 mo</td>
<td>12.5 mo</td>
<td></td>
</tr>
</tbody>
</table>

Hammel, ASCO 2013

LAP-07

Conclusions

- In LAPC patients with tumor controlled after 4 months of gemcitabine-based chemotherapy
  - CRT is not superior to continuing chemotherapy
  - Author's conclusion: Standard of care in LAPC should remain chemotherapy
    - CRT is an option
- Erlotinib in LAPC
  - Not beneficial
  - Increases toxicity
- Is there a subgroup who might benefit from CRT?
  - Correlative studies pending
LAP-07
Potential explanations for these results

- CRT is not superior to continuing chemotherapy
  - Is there any role for CRT in LAPC?
- There was inadequate radiation
  - Could we do better with IMRT, SBRT?
- There was inadequate chemotherapy
  - Could we do better with FOLFIRINOX, Gem-nab-P?
- There was inadequate chemo during RT
  - SCALOP trial: capecitabine better than gem with RT1
  - Are there better agents?
- Only a subset of patients can benefit
  - Can we use biomarkers like Smad4 to select them?

1. Mukherjee, Lancet Oncol 2013

Chemotherapy for metastatic pancreas cancer

- Metastatic PC has spread, usually to the liver, lungs, or abdominal cavity (peritoneum)

The goal of chemotherapy treatment for metastatic pancreas cancer is palliative:

- To shrink or stabilize disease
- To improve or prevent symptoms
- To prolong survival
The historical perspective: Chemotherapy for metastatic PC

Long-standing, well-deserved therapeutic nihilism

- Countless trials over several decades
- Many drugs and combinations tested
- Minimal to no activity observed

It’s 2015

This dismal outlook has changed
Now we have choices

The Options

- Gemcitabine
- Erlotinib
- Gemcitabine nab-Paclitaxel
- FOLFIRINOX

Key milestones in the development of new drugs for pancreatic cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-1996</td>
<td>The dark ages. Nothing works</td>
</tr>
<tr>
<td>1996</td>
<td>Gemcitabine improves survival compared with 5-FU. Gemcitabine is approved for PC</td>
</tr>
<tr>
<td>1996-2005</td>
<td>Many agents tested. No drug or drug combination is better than Gemcitabine</td>
</tr>
<tr>
<td>2005</td>
<td>Erlotinib + Gemcitabine modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC</td>
</tr>
<tr>
<td>2005-2009</td>
<td>More drugs tested. Many more negative trials</td>
</tr>
<tr>
<td>2010</td>
<td>FOLFIRINOX improves survival compared with Gemcitabine</td>
</tr>
<tr>
<td>2012</td>
<td>nab-Paclitaxel + Gemcitabine improves survival compared with Gemcitabine</td>
</tr>
</tbody>
</table>
We’ve made some progress:
Chemotherapy for pancreatic cancer: The dark ages

- Between 1991 and 1994, 25 investigational agents were evaluated in phase II trials for pancreatic cancer
- Median response rate: 0% (range 0-14%)
- Median survival: 3 months

Rothenberg, *Oncology* 1996

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Gemcitabine has a genuine, but modest impact on survival and quality of life

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>5-FU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>63</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Tumor Response</td>
<td>5.4%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>5.65 mo</td>
<td>4.4 mo</td>
<td>0.0025</td>
</tr>
<tr>
<td>1-year survival</td>
<td>18%</td>
<td>2%</td>
<td>0.0025</td>
</tr>
<tr>
<td>TTP</td>
<td>2.1 mo</td>
<td>0.9 mo</td>
<td></td>
</tr>
<tr>
<td>Clinical Benefit Response</td>
<td>24%</td>
<td>5%</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Burris, *JCO* 1997
Overall survival: Gemcitabine vs. 5-FU

Log-Rank Test

Gemcitabine 5.65 mo
5-FU 4.41 mo
p = 0.0025

We administer gemcitabine principally because it produces “clinical benefit”

Analgesic consumption
Pain intensity

Pain

Responder
Improvement in either or both, with no worsening
Stable
In both
Non-responder
Worsening in either

Performance status

Weight

Responder
≥7% ↑ weight
Non-responder
Stable or ↓ weight
Gemcitabine in context

- The cornerstone of PC therapy for many years

**Gemcitabine:**
- Minimal response rate
- Statistically significant but modest improvement in OS (4.4 vs. 5.6 months)
- Minimal toxicity
- Improves pain and PS and stabilizes weight
- No predictive biomarker
  - hENT1 data to date is negative in advanced disease\(^1\,^2\)

**The right patient:**
- Elderly patient with a poor PS
- The toxicity averse, symptomatic patient

\(^1\) Poplin *JCO* 2013  \(^2\) Ormanns, *EJC* 2014

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We should be able to do better than this!

How do we determine if there are any other drugs that work better than gemcitabine?
Until recently, the most common designs for randomized trials in pancreatic cancer patients

- Drug X
  vs. Gemcitabine

- Drug X plus Gemcitabine
  vs. Gemcitabine

Even though gemcitabine doesn’t work very well, it still works better than most other drugs
In phase III trials of Drug X vs. Gem, Gem usually wins—by ALOT

Exatecan vs. Gemcitabine

\[ p = 0.0933 \]

Gemcitabine also makes sick people feel better, and it is less toxic than most other drugs or drug combinations.
Two drugs should work better than one

Why not add other drugs to gemcitabine?

In phase III trials of Drug X + Gem vs. Gem, there is usually greater toxicity with the combination, but no survival difference

- IRINOGEM: median 6.3 months [4.7-7.5] – 1 year OS 21%
- GEM: median 6.6 months [5.2-7.8] – 1 year OS 22%

p = 0.789
Unfortunately, most of the time, more is not better.

Most combination treatments increase side effects, but don’t improve survival.

This pattern of super-imposable survival curves has been the most common outcome of phase III PC trials.
Despite “promising activity” of many Gem-doublets in phase II studies, they have not improved survival in phase III trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>G + X</th>
<th>G</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>bolus 5-FU</td>
<td>6.7 mo</td>
<td>5.4 mo</td>
<td>0.11</td>
</tr>
<tr>
<td>24-hr 5-FU</td>
<td>5.9 mo</td>
<td>6.2 mo</td>
<td>0.683</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>6.2 mo</td>
<td>6.3 mo</td>
<td>0.85</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>8.4 mo</td>
<td>7.3 mo</td>
<td>0.314</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>6.3 mo</td>
<td>6.6 mo</td>
<td>0.789</td>
</tr>
<tr>
<td>Exatecan</td>
<td>6.7 mo</td>
<td>6.2 mo</td>
<td>0.52</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>7.6 mo</td>
<td>6.0 mo</td>
<td>0.12</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>9.0 mo</td>
<td>7.1 mo</td>
<td>0.13</td>
</tr>
</tbody>
</table>

This bleak outlook **finally** changed in 2005 with a Canadian trial
The NCIC PA3 trial demonstrated a modest improvement in survival for gemcitabine + erlotinib

Gemcitabine
Erlotinib
100 or 150 mg po qd

569 pts

Gemcitabine
Placebo

Statistics: 80% power to detect a 33% ↑ survival, α=0.05

Moore, JCO 2007

Erlotinib (Tarceva) inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase

EGFR (HER-1)

Signaling Cascade

Nucleus

Angiogenesis

Proliferation

Survival
### Overall Survival

![Graph showing overall survival](image)

- **HR = 0.82**
- **95% CI, 0.69-0.99**
- **P = 0.038**

**Survival probability**

- **Gemcitabine + erlotinib**
  - Median = 6.24 mo

- **Gemcitabine + placebo**
  - Median = 5.91 mo

*Adjusted for PS, pain, and disease extent at randomization.

### Gemcitabine + erlotinib: A modest improvement

<table>
<thead>
<tr>
<th></th>
<th>GE</th>
<th>G</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>285</td>
<td>284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>8.6%</td>
<td>8.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median survival</td>
<td>6.24</td>
<td>5.91</td>
<td>0.82</td>
<td>0.038</td>
</tr>
<tr>
<td>1-year survival</td>
<td>23%</td>
<td>17%</td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>3.75</td>
<td>3.55</td>
<td>0.77</td>
<td>0.004</td>
</tr>
<tr>
<td>QOL (EORTC QLQ-C30)</td>
<td></td>
<td>Better on placebo</td>
<td>(↑ diarrhea on GE)</td>
<td></td>
</tr>
<tr>
<td>GE: Cost/YLG</td>
<td></td>
<td>$500K1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In 2005, the FDA approved erlotinib in combination with gemcitabine for advanced PC

Can a biomarker predict the activity of erlotinib?

KRAS mutations
- Confer resistance to EGFR inhibitors
- Very common in PC (75-90%)
  - The highest incidence of any cancer

Activating EGFR mutations
- Rare (<4%)

Molecular subset analysis of PA3 trial
- KRAS status did not predict a survival benefit for gemcitabine + erlotinib

da Cunha Santos, Cancer 2010

Severity of rash correlates with survival

<table>
<thead>
<tr>
<th>Grade</th>
<th>N</th>
<th>Median survival</th>
<th>1-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79</td>
<td>5.29</td>
<td>16%</td>
</tr>
<tr>
<td>1</td>
<td>108</td>
<td>5.75</td>
<td>11%</td>
</tr>
<tr>
<td>≥2</td>
<td>103</td>
<td>10.51</td>
<td>43%</td>
</tr>
</tbody>
</table>

HR [Rash] = 0.71
p < 0.0001
Dose escalation to rash
The RACHEL study

In patients with grade 0-1 rash after 4 weeks of gemcitabine + erlotinib:
• Does escalating the erlotinib dose to >100 mg improve survival?

<table>
<thead>
<tr>
<th></th>
<th>Standard dose erlotinib (N=75)</th>
<th>Dose-escalated erlotinib (N=70)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash ≥ Grade 2</td>
<td>9%</td>
<td>41%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>8.4</td>
<td>7.0</td>
<td>0.2026</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>4.5</td>
<td>3.5</td>
<td>0.6298</td>
</tr>
</tbody>
</table>

Dose-escalating erlotinib increases rash, not survival
Van Cutsem, 2012

Gemcitabine + Erlotinib in context
• PA3 is the 1st randomized trial to demonstrate that any drug added to Gem prolongs survival in PC

Erlotinib + gemcitabine produces:
• A statistically significant improvement in OS (HR 0.82) and PFS (HR 0.77)
• Modest toxicity
• No improvement in QOL
• Substantial cost ($500K/YLG)
• No biomarker to select those most likely to benefit

Questions:
• How clinically meaningful are these results?
• Is the modest benefit worth the expense & toxicity?
Who is the best patient for this regimen?
Over the next 5 years, several more negative phase III trials were reported

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>N</th>
<th>G + X (mo)</th>
<th>G (mo)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMCAP</td>
<td>Capecitabine</td>
<td>533</td>
<td>7.1</td>
<td>6.2</td>
<td>0.08</td>
</tr>
<tr>
<td>GIP</td>
<td>Cisplatin</td>
<td>400</td>
<td>7.2</td>
<td>8.3</td>
<td>0.38</td>
</tr>
<tr>
<td>E6201</td>
<td>Oxaliplatin</td>
<td>832</td>
<td>5.7</td>
<td>4.9</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>FDR Gem</td>
<td></td>
<td>6.2</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>CALGB 80303</td>
<td>Bevacizumab</td>
<td>602</td>
<td>5.8</td>
<td>5.9</td>
<td>0.95</td>
</tr>
<tr>
<td>S0205</td>
<td>Cetuximab</td>
<td>704</td>
<td>6.4</td>
<td>5.9</td>
<td>0.14</td>
</tr>
<tr>
<td>GemAx</td>
<td>Axitinib</td>
<td>632</td>
<td>8.5</td>
<td>8.3</td>
<td>0.54</td>
</tr>
<tr>
<td>AViTA</td>
<td>Bevacizumab</td>
<td>607</td>
<td>7.1</td>
<td>6.0</td>
<td>0.21</td>
</tr>
</tbody>
</table>

CALGB 80303: Gemcitabine +/- Bevacizumab
Once again, no survival difference

Bevacizumab 5.8 mo
Placebo 5.9 mo
P = 0.95
Have we learned anything from these negative trials? A meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>HR survival</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + X</td>
<td>0.91</td>
<td>0.004</td>
</tr>
<tr>
<td>Gem + platinum</td>
<td>0.85</td>
<td>0.01</td>
</tr>
<tr>
<td>Gem + fluoropyrimidine</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Gem + other cytotoxic</td>
<td>0.99</td>
<td>0.08</td>
</tr>
<tr>
<td>Good PS (≥ 90%)</td>
<td>0.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Poor PS (60-80%)</td>
<td>1.08</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- **Gem + a platinum or a fluoropyrimidine:**
  - Modestly superior to gem alone
- **Good PS pts:**
  - Survival benefit from combination chemo
- **Poor PS pts:** No benefit from combination chemo

Heinemann, BMC Cancer 2008

Then came the study that changed the way we think about chemotherapy for pancreatic cancer
In 2010: A substantial treatment advance
The PRODIGE 4 - ACCORD 11 trial

**Randomize**

**FOLFIRINOX**
Primary endpoint: OS

**Gemcitabine**

No prior chemo
PS 0-1
< 76 yrs
Measurable metastatic disease
T. bili < 1.5 x ULN

342 patients

Conroy, ASCO 2010, NEJM 2011

**Stratification:**
- Center
- PS: 0 vs. 1
- 1° tumor location: head vs. other

**Progression-free survival**

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

**FOLFIRINOX:** 6.4 mo

**Gemcitabine:** 3.3 mo

p<0.0001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Folfirinox</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
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<td>27</td>
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<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Probability**

**Months**

0 3 6 9 12 15 18 21 24 27 30 33 36
**Overall survival**

![Overall survival graph](image)

- **FOLFIRINOX**: 11.1 mo
- **Gemcitabine**: 6.8 mo

Stratified Log-rank test, p<0.0001

HR=0.57 : 95%CI [0.45-0.73]

**Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>G</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>171</td>
<td>171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response</td>
<td>31.6%</td>
<td>9.4%</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.6%</td>
<td>41.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control (PR+SD)</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>11.1</td>
<td>6.8</td>
<td>0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year survival</td>
<td>48.4%</td>
<td>20.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 month survival</td>
<td>18.6%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>6.4</td>
<td>3.3</td>
<td>0.47</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### FOLFIRINOX vs. Gemcitabine

**Selected grade 3 and 4 toxicities**

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>G</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>45.7%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5.4%</td>
<td>1.2%</td>
<td>0.03</td>
</tr>
<tr>
<td>G-CSF usage</td>
<td>42.5%</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9.1%</td>
<td>3.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>↑ ALT</td>
<td>7.3%</td>
<td>20.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12.7%</td>
<td>1.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23.6%</td>
<td>17.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14.5%</td>
<td>8.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>32.5%</td>
<td>3%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Although they had more chemotherapy-related side effects, patients who received FOLFIRINOX felt much better for much longer than patients who received Gemcitabine.
Finally, a big step forward

After so many negative trials of gemcitabine doublets, the unprecedented outcomes achieved with FOLFIRINOX are a major treatment advance for good PS pancreatic cancer patients.

No other randomized study has ever:

- Achieved a median survival of nearly a year
- Demonstrated such a high response rate

Despite substantial, but manageable toxicities, FOLFIRINOX also helps patients feel better for longer than if they received gemcitabine (a drug used principally for its impact on symptoms)

- Remarkably, it’s even cost-effective

A paradigm shift

- **This is a true paradigm shift**
  - For the first time, an oncologist can confidently tell a pancreatic cancer patient who has a good performance status that they are very likely to obtain disease control with chemotherapy

- **It has been a very long journey**
  - We are finally beginning to make progress against this devastating disease
FOLFIRINOX in context

- Significantly improves median OS
  - 11.1 vs. 6.8 mo, HR 0.57, p<0.0001
- Significantly improves PFS
  - 6.4 vs. 3.3 mo HR 0.47, p<0.0001
- Yields a meaningful delay in worsening of QOL
- Is cost-effective
- Is more toxic:
  - 46% grade 3−4 neutropenia, 5% febrile neutropenia
  - Vigilant patient selection, education, monitoring are essential
- Impact of routine dose modifications unclear
- No biomarker identified to date
- Who is the optimal patient for FOLFIRINOX?

Soon afterwards, another study demonstrated that another new combination is more active than gemcitabine
The MPACT Trial

861 patients
- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

Primary endpoint: Overall survival

151 sites enrolled 861 patients on 3 continents over 3 years

608 events, 90% power to detect OS;
HR = 0.769 (2-sided α = 0.049)
Treat until progression
CT scans Q8 wks
PET scan subset: baseline, wks 8, 16
CA19-9: at baseline and Q8 wks

von Hoff, ASCO 2013, NEJM 2013

Progression-free survival

PFS, months

<table>
<thead>
<tr>
<th></th>
<th>nab-P + Gem</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (95% CI)</td>
<td>5.5 (4.47–5.95)</td>
<td>3.7 (3.61–4.04)</td>
</tr>
<tr>
<td>HR</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.581–0.821)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.000024</td>
<td></td>
</tr>
</tbody>
</table>

Pts at Risk

<table>
<thead>
<tr>
<th></th>
<th>nab-P + Gem</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>431</td>
<td>281</td>
<td>122</td>
</tr>
<tr>
<td>430</td>
<td>209</td>
<td>51</td>
</tr>
</tbody>
</table>

PFS Rate at

<table>
<thead>
<tr>
<th></th>
<th>nab-P + Gem</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>44%</td>
<td>25%</td>
</tr>
<tr>
<td>12 months</td>
<td>16%</td>
<td>9%</td>
</tr>
</tbody>
</table>

% Increase

<table>
<thead>
<tr>
<th></th>
<th>nab-P + Gem</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>
Overall survival

<table>
<thead>
<tr>
<th>Months</th>
<th>Pts at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>431 nab-P + Gem: 431, Gem: 430</td>
</tr>
<tr>
<td>3</td>
<td>357</td>
</tr>
<tr>
<td>6</td>
<td>269</td>
</tr>
<tr>
<td>9</td>
<td>169</td>
</tr>
<tr>
<td>12</td>
<td>108</td>
</tr>
<tr>
<td>15</td>
<td>67</td>
</tr>
<tr>
<td>18</td>
<td>40</td>
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</tr>
<tr>
<td>24</td>
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</tr>
<tr>
<td>27</td>
<td>9</td>
</tr>
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<td>30</td>
<td>4</td>
</tr>
<tr>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
</tr>
</tbody>
</table>

Proportion of Survival

Median OS, months

- nab-P + Gem: 8.5 (7.89–9.53)
- Gem: 6.7 (6.01–7.23)

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

Efficacy: nab-Paclitaxel-Gemcitabine vs. Gemcitabine

<table>
<thead>
<tr>
<th></th>
<th>nab-G</th>
<th>G</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>431</td>
<td>430</td>
<td></td>
</tr>
<tr>
<td>Objective Response</td>
<td>23%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>25%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Disease control (PR+SD)</td>
<td>48%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Median survival (mo)</td>
<td>8.5</td>
<td>6.7</td>
<td>0.72</td>
</tr>
<tr>
<td>1-year survival</td>
<td>35%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>18-month survival</td>
<td>16%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>24-month survival</td>
<td>9%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>5.5</td>
<td>3.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Median duration on treatment (mo)</td>
<td>3.9</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>
Toxicity: *nab*-Paclitaxel-Gemcitabine vs. Gemcitabine

<table>
<thead>
<tr>
<th></th>
<th>Nab-G</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3%</td>
<td>1%</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>Diarrhea</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>G-CSF usage</td>
<td>26%</td>
<td>15%</td>
</tr>
</tbody>
</table>

The MPACT trial in context

1<sup>st</sup> randomized trial to demonstrate that a cytotoxic agent added to Gem prolongs survival in PC

*nab*-Paclitaxel + Gemcitabine
- Significantly improves OS
  - 8.5 vs. 6.7 mo, HR 0.72, \( P = 0.000015 \)
- Significantly improves PFS
  - 5.5 vs. 3.7 mo HR 0.69, \( P = 0.000024 \)
- More toxic
  - 38% grade 3<sup>+</sup> neutropenia, 17% grade 3<sup>+</sup> neuropathy, 17% grade 3<sup>+</sup> fatigue
- QOL:
  - Not collected prospectively, Q-TWIST favorable
- Cost effectiveness: Not cost-effective?
- Biomarker: SPARC not predictive

Who is the optimal patient for Gem-nab-Paclitaxel?
We’re not accustomed to having good treatment choices in PC

FOLFIRINOX or Gemcitabine-nab-paclitaxel:
How do you decide which combination is best for which patient?
• By understanding the current data
  • And its limitations
• No biomarker can predict which patient will respond to a particular treatment
• No randomized trial compares these 2 regimens
  – Cross-trial comparisons can be problematic

What factors into our choice of a given regimen?

Understand the data
Individualize therapy for each patient
Patient-related factors that may affect choice of regimen

- Age
- Performance status
- Co-morbidity
- Compliance
- Travel distance
- Tolerance for side effects
- Tumor biomarkers
- Organ function

Regimen-related factors that may affect choice of treatment

- QOL
- Response rate
- Overall survival
- Complexity
- Toxicity
- Cost
- PFS
Physician-related factors that may affect choice of regimen

- Ability to closely monitor the patient
- Experience with a particular regimen
- Expertise in toxicity management

Chemotherapy for advanced PC: Where are we now?

- Gemcitabine
  - Cornerstone of care for many years
  - Improves quality of life, modestly improves survival
- Gemcitabine + erlotinib
  - Marginally improves survival
- Meta-analysis
  - Suggests that good PS pts benefit from Gem + a platinum or a fluoropyrimidine
### Chemotherapy for advanced PC: Where are we now?

- **FOLFIRINOX**
  - Improves RR, PFS, OS in good PS pts
  - More toxic: patient selection and monitoring essential

- **Gemcitabine + nab-Paclitaxel**
  - Improves RR, PFS, OS
  - Not as active as FOLFIRINOX, slightly less toxic

---

**Although we are making incremental progress in the treatment of advanced pancreatic cancer, new drugs and new approaches are still urgently needed!**
There are fewer research $\textdollar$ allocated to study pancreas cancer compared with other major cancers

Hopefully this will be changing soon!

January is National Pancreatic Cancer Clinical Trials Awareness Month
Fewer than 5% of all pancreatic cancer patients enroll in clinical trials

Hoos et al, JCO 2013

We need to do better than this

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goal</th>
<th>Patients</th>
<th>Prior treatment</th>
<th>Placebo?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Dose and side effects</td>
<td>Any cancer</td>
<td>Usually unlimited</td>
<td>No</td>
</tr>
<tr>
<td>II</td>
<td>Determine effectiveness</td>
<td>All pts must have the same cancer</td>
<td>All pts must the same number of prior treatments, usually 0, 1 or 2</td>
<td>Not usually</td>
</tr>
<tr>
<td>III</td>
<td>Compare to a standard regimen</td>
<td></td>
<td></td>
<td>Usually</td>
</tr>
</tbody>
</table>
How do we select new agents to test in clinical trials for pancreas cancer?

We look for targets with intriguing data in the laboratory.

Caveat: Promising preclinical data has led to many disappointing results in patients.

A core set of 12 signaling pathways are genetically altered in most PC. Some of these pathways, or their downstream mediators, may be potential therapeutic targets.
How do we select new drugs to test in PC patients?

The choice of drug for a given clinical trial is ultimately based on:
• Availability of agents for clinical testing against a target of interest
• Phase I single-agent and combination safety data
• Willingness of a drug company to test drugs in this disease

Some types of drugs being evaluated for PC: Chemotherapy

Cytotoxic chemotherapy:
• These drugs (such as gemcitabine) affect the DNA of the cancer cell in various ways
  – MM-398: A nano-liposomal irinotecan

Drugs to enhance the uptake of chemotherapy into the pancreas:
– These agents target the dense stroma around the tumor that acts as a barrier to protect the cancer cells from chemotherapy
  – Hedgehog pathway inhibitors (worked in the lab, not in patients):
    • GDC-0449, IPI-926
  – Pegylated Hyaluronidase:
    • PEGPH20
Some types of drugs being evaluated for PC: Targeted therapy

Targeted therapy:
• These drugs (such as erlotinib) affect signaling pathways that turn cell growth on and off
• Many early trials were unsuccessful, likely because they were offered to unselected patients
• Targeted agents may be more effective in subsets of patients who have the specific abnormalities in their tumors that are targeted by those drugs
  – Targeting abnormal DNA damage repair in patients with BRCA 1 and 2 mutations
    • PARP inhibitors: veliparib, olaparib
  – Targeting Janus kinase (JAK) in patients with high CRP
    • Ruxolitinib

Some types of drugs being evaluated for PC: Immunotherapy

Immunotherapy
• Vaccines
  – Stimulate the immune system to attack the cancer
    • GVAX/CRS-207
• Immune checkpoint inhibitors
  – Take off the brakes in the immune system so that it can attack the cancer
    • Several agents in early trials
Hopefully someday, these headlines will be for pancreatic cancer drugs.

Thank you for your participation.

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

www.pancan.org or wagehope.org