Systemic therapy for Advanced Pancreatic Cancer

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Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

By Howard A. Burris III, Malcolm J. Moore, John Andersen, et al

Gemcitabine vs 5-FU in Unresectable Pancreatic Cancer: Clinical Trial Design

Patients with untreated, unresectable pancreatic cancer (75% stage IV), KPS ≤ 80, morphine ≥ 10 mg/d, MPAC pain intensity score ≥ 20 (N = 126)

**Gemcitabine**
1000 mg/m² weekly x 7, off x 1, then weekly x 3 of 4 weeks
(n = 63)

**5-FU**
600 mg/m² weekly
(n = 63)

Gemcitabine vs 5-FU in Unresectable Pancreatic Cancer: Outcomes

- Outcomes in gemcitabine arm vs 5-FU arm
  - Clinical benefit response:* 23.8% vs 4.8% ($P = .002$)
  - Median survival time: 5.7 vs 4.4 months ($P = .003$)
  - 1-year overall survival rate: 18% vs 2%

*Clinical benefit response (primary study outcome) is a composite score of pain, performance status, and weight.

This study established Gemcitabine as a reasonable option in advanced symptomatic patients
Cytotoxic Combinations With Gemcitabine

- Many regimens have been evaluated
  - Platinum agents
  - Taxanes
  - Topoisomerase inhibitors
  - Fluoropyrimidines (oral and intravenous)

- Large, well-designed, randomized clinical trials
- No significant improvements in outcomes
# Gemcitabine Combination Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Regimen</th>
<th>Response Rate, %</th>
<th>Median Survival, mos</th>
<th>1-Year Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocha Lima CM, et al(^1)</td>
<td>Gem alone vs gem + irinotecan</td>
<td>4.4</td>
<td>6.6</td>
<td>22</td>
</tr>
<tr>
<td>Oettle H, et al(^2)</td>
<td>Gem alone vs gem + pemetrexed</td>
<td>7.1</td>
<td>6.3</td>
<td>20</td>
</tr>
<tr>
<td>Louvet C, et al(^3)</td>
<td>Gem alone vs gem + oxaliplatin</td>
<td>17.3</td>
<td>7.1</td>
<td>28</td>
</tr>
<tr>
<td>Colucci G, et al(^4)</td>
<td>Gem alone vs gem + cisplatin</td>
<td>9.2</td>
<td>5</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Gemcitabine Plus Capecitabine

- 1 positive study
- Subsequent study using a different dosing regimen showed no benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Regimen</th>
<th>Median Survival, mos</th>
<th>1-Year Survival, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrmann R, et al(^1) (n = 319)</td>
<td>Gem alone vs gem/capecitabine(*)</td>
<td>7.2</td>
<td>31</td>
<td>.234</td>
</tr>
<tr>
<td>Cunningham D, et al(^2) (n = 533)</td>
<td>Gem alone vs gem/capecitabine(†)</td>
<td>6.0</td>
<td>19</td>
<td>.026</td>
</tr>
</tbody>
</table>

\*Gemcitabine 1000 mg/m\(^2\) weekly × 2 q3 weeks; capecitabine 1300 mg/m\(^2\)/day × 14 q3 weeks.

\(†\)Gemcitabine 1000 mg/m\(^2\) weekly × 3 q4 weeks; capecitabine 1660 mg/m\(^2\)/day for 21 days q4 weeks.

Combination Chemo for Advanced Pancreatic Cancer: Current Status

• Benefit will be small
  – One positive study: gemcitabine plus capecitabine
  – Many more negative trials

• Alternative therapeutic strategies
  – Potentially more useful vs further studies of chemotherapy combinations

Molecular Pathogenesis of Pancreatic Cancer

- Genetic changes important in propagating pancreatic cancer have been well described\(^1\)
- Even at earliest clinical stage, pancreatic cancer is a molecularly advanced malignancy with numerous chromosomal aberrations\(^2\)
- More chromosomal losses described than gains
  - Highlights importance of tumor suppressor genes

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# Oncogenes in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Relevance</th>
</tr>
</thead>
</table>
| K-ras$^1$          | Noted in 75% to 90% of cases  
Also identified in premalignant lesions and chronic pancreatitis  
Considered signature defect of pancreatic cancer |
| Sonic Hedgehog$^2$ | Crucial role in embryological signaling  
Evolving role in pancreas cancer |
| AURKA$^3$          | Encodes Aurora-A kinase  
Overamplification leads to chromosomal instability |

### Tumor Suppressor Genes in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Tumor Suppressor Gene</th>
<th>Relevance</th>
</tr>
</thead>
</table>
| CDKN2A/p16\(^1,2\)   | Normal function induces cell cycle arrest (with Rb)  
Functional loss is an early event and enhances oncogenic effect of K-ras |
| SMAD4\(^2,3\)         | Encodes transcription factor; lost in 50% of cases  
May also potentiate K-ras phenotype |
| p53\(^4,5\)           | Role in cell cycle arrest and apoptosis  
Loss contributes to chromosomal instability |

Molecular Targets in Pancreatic Cancer

Growth Factor Ligand
(EGF, VEGF)

ECM
Integrin Homodimer
ras
FAK
Src
PI3K
Akt
EGF Receptor
Pro-MMP

Regulation of Gene Transcription

Nucleus
Early Trials of Targeted Agents: Negative Results

• Ras-farnesyltransferase inhibitors
  – Gemcitabine vs gemcitabine plus tipifarnib\(^1\)

• Matrix metalloproteinase inhibitors
  – Gemcitabine vs gemcitabine plus marimastat\(^2\)
  – Gemcitabine vs tanomastat (BAY 12-9566)\(^3\)

Failure of FTI

• A likely explanation for the failure of this drug to demonstrate significant clinical activity is that Ras proteins can also be activated by geranylgeranylation, that is not inhibited by tipifarnib.

• Additionally, preclinical work has suggested that FTIs are less effective against the mutated K-ras proteins commonly found in pancreatic cancer, but more effective in the setting of H-ras mutations.
Epidermal Growth Factor Receptor (EGFR)

- EGFR is 1 of 4 members of receptor tyrosine kinase family
- Ligand (EGF) binding results in dimerization and receptor autophosphorylation/activation
- Activated EGFR mediates downstream signaling
  - Promotes survival, proliferation, and motility
- Aberrant EGFR signaling implicated in numerous cancers
- EGFR overexpression in pancreatic cancer correlates with poor prognosis and chemoresistance

EGFR Dimerization After Ligand Binding

- EGFR Dimerization
- Proliferation
- Resistance to Apoptosis
- Angiogenesis
- Migration and Invasion
EGFR-Targeted Approaches

- Anti-EGFR Blocking Antibodies (eg, Cetuximab)
- Anti-Ligand Blocking Antibodies
- TK Inhibitors (Gefitinib, Erlotinib)
- Ligand-Toxin Conjugates
- Antibody-Toxin Conjugates

Erlotinib

- Small-molecule tyrosine kinase inhibitor of EGFR
- Competes with ATP for binding to kinase domain
- Preclinical studies
  - Growth inhibition in pancreatic cancer cell lines\(^1\)
  - Additive effects with cytotoxic agents, including gemcitabine\(^2\)
- Adverse effects
  - Rash
  - Diarrhea

Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, et al.

Key eligibility criteria

• Locally advanced or metastatic adenocarcinoma of the pancreas
• Age $\geq$ 18 years
• PS 0–2
• Measurable or non-measurable disease
• Prior radiotherapy for local disease allowed
• No prior chemotherapy, except for 5-FU or gemcitabine as a radiosensitiser
• HER1/EGFR-positive status not required
Study schema

Stratified by:
- Centre
- ECOG PS (0/1 vs 2)
- Stage of disease (locally advanced vs distant metastases)  
  (n=569)

R A N D O M I Z E

Gemcitabine 1,000mg/m² i.v. +
Erlotinib 100/150mg/day p.o.  
(n=285)

Gemcitabine 1,000mg/m² i.v. +
placebo 100/150mg/day p.o.  
(n=284)

Primary End-Point – OS
Secondary – PFS, QOL, RR, Toxicity

*1:1 randomisation
**Patient characteristics**

- 569 patients randomised
  - 521 patients at 100mg or placebo
  - 48 patients at 150mg or placebo

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Tarceva (n=285)</th>
<th>Placebo (n=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Female/male (%)</td>
<td>52/48</td>
<td>43/57</td>
</tr>
<tr>
<td>PS 0/1/2 (%)</td>
<td>30/51/19</td>
<td>30/52/18</td>
</tr>
<tr>
<td>Locally advanced/metastatic (%)</td>
<td>24/76</td>
<td>25/75</td>
</tr>
<tr>
<td>Pain score ≤20/&gt;20/unknown (%)</td>
<td>46/51/3</td>
<td>45/53/2</td>
</tr>
<tr>
<td>Measurable disease (%)</td>
<td>94</td>
<td>92</td>
</tr>
<tr>
<td>USA/Canada/RoW (%)</td>
<td>38/20/42</td>
<td>36/21/43</td>
</tr>
</tbody>
</table>
**OS**

- Erlotinib (n = 285)
- Median = 6.24 months
- 1-year survival = 23%

- Placebo (n = 284)
- Median = 5.91 months
- 1-year survival = 17%

HR = 0.82
95% CI (0.69 to 0.99)
P = .038

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**PFS**

- Erlotinib (n = 285)
- Median = 3.75 months

- Placebo (n = 284)
- Median = 3.55 months

HR = 0.77
95% CI (0.64 to 0.92)
P = .004
### OS by pre-Rx characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib:Placebo</td>
<td>0.82 (0.69 to 0.99)</td>
<td>569</td>
</tr>
<tr>
<td>Age ≤ 65</td>
<td>0.75 (0.58 to 0.96)</td>
<td>301</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>0.96 (0.74 to 1.24)</td>
<td>268</td>
</tr>
<tr>
<td>ECOG PS = 0 or 1</td>
<td>0.87 (0.71 to 1.06)</td>
<td>462</td>
</tr>
<tr>
<td>ECOG PS = 2</td>
<td>0.61 (0.41 to 0.92)</td>
<td>106</td>
</tr>
<tr>
<td>Female</td>
<td>0.98 (0.75 to 1.28)</td>
<td>271</td>
</tr>
<tr>
<td>Male</td>
<td>0.74 (0.58 to 0.95)</td>
<td>298</td>
</tr>
<tr>
<td>Pain score ≤ 20</td>
<td>0.71 (0.54 to 0.93)</td>
<td>258</td>
</tr>
<tr>
<td>Pain score &gt; 20</td>
<td>1.00 (0.78 to 1.27)</td>
<td>296</td>
</tr>
<tr>
<td>Local advanced</td>
<td>0.94 (0.63 to 1.39)</td>
<td>138</td>
</tr>
<tr>
<td>Distant metastatic</td>
<td>0.79 (0.65 to 0.97)</td>
<td>431</td>
</tr>
<tr>
<td>EGFR positive</td>
<td>0.80 (0.50 to 1.26)</td>
<td>86</td>
</tr>
<tr>
<td>EGFR negative</td>
<td>0.81 (0.49 to 1.32)</td>
<td>76</td>
</tr>
<tr>
<td>Sample not available</td>
<td>0.85 (0.69 to 1.05)</td>
<td>407</td>
</tr>
</tbody>
</table>
PA.3: overall survival according to grade of rash

HR (rash) = 0.71, p < 0.0001

Median survival (months)  
Grade 0 (n=79) 5.29  
Grade 1 (n=108) 5.75  
Grade ≥2 (n=103) 10.51

1-year survival (%)  
Grade 0 (n=79) 16  
Grade 1 (n=108) 11  
Grade ≥2 (n=103) 43

<table>
<thead>
<tr>
<th>Variable</th>
<th>Erlotinib and Gemcitabine (n = 282)</th>
<th>Placebo and Gemcitabine (n = 280)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>100 mg/d erlotinib and placebo</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>150 mg/d erlotinib and placebo</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>Specific toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>89</td>
<td>15</td>
</tr>
<tr>
<td><strong>ILD-like syndrome</strong></td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Infection (any)</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Rash</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dose reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib and placebo (n = 562)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>100 mg (n = 515)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>150 mg (n = 47)</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
NCIC-CTG PA.3 Study: Conclusions

- First demonstration of clinical benefit of an EGFR tyrosine kinase inhibitor in combination with chemotherapy
- Proof-of-concept of EGFR inhibition
- Benefit from gemcitabine plus erlotinib likely restricted to a subset of patients
  - 10% increase in tumor control
    - Strong association with skin rash
  - How to identify this subset of patients?
- Increased interest in clinical evaluation of other targeted therapies
First-Line Gemcitabine ± Cetuximab: SWOG S0205 Phase III Trial

Stratified by disease status, Zubrod PS (0/1 vs 2), prior pancreatectomy

Patients with locally advanced or metastatic pancreatic adenocarcinoma (N = 735)

Gemcitabine 1000 mg/m²/week for 7 of 8 weeks, then 3 of every 4 weeks (n = 366)

Gemcitabine 1000 mg/m²/week for 7 of 8 weeks, then 3 of every 4 weeks + Cetuximab 400 mg/m² Week 1, then 250 mg/m² weekly (n = 369)

Primary endpoint: overall survival

First-Line Gemcitabine ± Cetuximab: SWOG S0205 Results

- No significant difference in overall or progression-free survival between gemcitabine vs gemcitabine/cetuximab arms
- Time to treatment failure prolonged with gemcitabine/cetuximab ($P = .0014$)
- No significant difference in response rates between arms
- No major toxicity differences between arms
  - Slightly higher incidence of grade 3/4 rash and allergic reaction in gemcitabine/cetuximab arm

Philip PA, et al. ASCO 2007. Abstract LBA4509
Antiangiogenic Therapy: Targeting the Tumor and Endothelial Cells

• Bevacizumab
  – Monoclonal antibody
  – Binds angiogenic protein VEGF
  – Mechanism:
    • Inhibits endothelial cells from responding to VEGF
Patients with advanced pancreatic adenocarcinoma (N = 602)

**Gemcitabine ± Bevacizumab**: CALGB 80303 Phase III Trial

Stratified by disease status, ECOG PS (0/1 vs 2), prior radiotherapy

- **Bevacizumab** 10 mg/kg, Days 1 and 15 + **Gemcitabine** 1000 mg/m², Days 1, 8, and 15 of 28-day cycle (n = 302)

- **Placebo**, Days 1 and 15 + **Gemcitabine** 1000 mg/m², Days 1, 8, and 15 of 28-day cycle (n = 300)

Primary endpoint: 35% improvement in survival (from 6 to 8.1 months)

Gemcitabine ± Bevacizumab: CALGB 80303 Results

- No significant difference in overall or progression-free survival between gemcitabine vs gemcitabine/bevacizumab arms
  - Median survival: 6.1 vs 5.8 months, respectively
- Patients with locally advanced disease had longer overall survival vs patients with metastatic disease
  - 9.9 vs 5.7 months, respectively (HR: 1.4; \( P = .009 \))
- Patients with better PS had longer overall survival (PS 0 > PS 1 > PS 2)
  - 8.0 vs 4.8 vs 2.8 months, respectively (\( P = .0001 \))
- No significant difference in response rates between arms
- No major toxicity differences between arms, except
  - Higher incidence of hypertension and proteinuria in gemcitabine/cetuximab arm

AVITA: Tarceva + gemcitabine ± Avastin – a phase III study in advanced pancreatic cancer

- Previously untreated metastatic pancreatic cancer (n=600)
- Tarceva gemcitabine Avastin (5mg/kg every 2 weeks)
- Tarceva gemcitabine placebo
- Primary endpoint: overall survival
- Secondary endpoints include progression-free survival and response rate
- Initial interim analysis will be performed after first 200 patients have completed 8 weeks of treatment

*No cross over will be permitted
Antisense Therapeutics for Tumor Treatment: The TGF-beta2 Inhibitor AP 12009 in Clinical Development Against Malignant Tumors

NF-κB as a Molecular Target in the Therapy of Pancreatic Carcinoma

Immunotherapeutic Approaches in Pancreatic Cancer

Src Kinase and Pancreatic Cancer
Pancreatic Cancer Therapy: Conclusions

• Clinical progress has been made in the management of pancreatic cancer during the past 10 years
• In metastatic disease, 1-year survival rates have improved from < 2% to approximately 20%
• Adjuvant therapy improves disease-free survival
• At least 2 agents positively affecting survival have been identified
  – Gemcitabine
  – Erlotinib
  – Oral fluoropyrimididine?
Thank you