Metastatic Pancreatic Cancer
Systemic Treatment and Potential Advances

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Overview

• Current Therapeutic Options
  1\textsuperscript{st} Line
  2\textsuperscript{nd} Line

• Molecular Profiling and Advances

• Case
1st Line Chemotherapy for Metastatic Disease
5-fluorouracil

- 1950s: 5-FU mainstay treatment
- Survival Benefit of ~3 months vs. BSC
- Multiple combinations attempted
  - Doxorubicin
  - Mitomycin C
  - Cyclophosphamide
  - Methotrexate
  - Vincristine
  - Cisplatin

All increased toxicity with no survival benefit

Moertel CG. Chemotherapy of gastrointestinal cancer
Gemcitabine

• First drug to increase OS vs. 5-FU
• Improved clinical benefit rate (24% vs. 4%)
• Improved mOS (5.6 vs. 4.4 months) and 1 year survival rate (18% vs. 2%)
• Improved Response Rate (5% vs. 0%)

1990s-2010s multiple trials attempted to improve on single agent gemcitabine

<table>
<thead>
<tr>
<th>Chemo</th>
<th>No. Pts</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem+ Capecitabine</td>
<td>533</td>
<td>13.9% vs. 8.4% PFS rate at 12 months (p=0.004)</td>
<td>11 vs. 9.2 (p=0.038)</td>
<td>Cunningham et al. (2009)</td>
</tr>
<tr>
<td>Gem+ Cisplatin</td>
<td>400</td>
<td>3.9 vs. 3.8 (p=0.38)</td>
<td>8.3 vs. 7.2 (p=0.80)</td>
<td>Colucci et al. (2010)</td>
</tr>
<tr>
<td>Gem+ Oxaliplatin</td>
<td>313</td>
<td>5.8 vs. 3.7 (p=0.04)</td>
<td>9 vs. 7.1 (p=0.13)</td>
<td>Louvet et al. (2005)</td>
</tr>
<tr>
<td>Gem+ Irinotecan</td>
<td>342</td>
<td>3.5 vs. 3 (p=0.352)</td>
<td>6.3 vs. 6.6 (p=0.789)</td>
<td>Rocha Lima et al. (2004)</td>
</tr>
<tr>
<td>Gem+ Pemetrexed</td>
<td>565</td>
<td>3.9 vs. 3.3 (p=0.1109)</td>
<td>6.2 vs. 6.3 (p=0.8477)</td>
<td>Oettle et al. (2005)</td>
</tr>
</tbody>
</table>
Meta-analysis of clinical studies

### Overall survival analysis:

**Gemcitabine versus Gemcitabine-based combination (Combo) chemotherapy,**

HR= 0.91, 95% CI 0.85-0.97

Sultana et al. JCO 2007;25:2607-2615
FOLFIRINOX

- Phase III ACCORD study 1st meaningful survival benefit over single agent gemcitabine
- FOLFIRINOX vs. Gemcitabine
- n= 342
- Primary endpoint= OS

Overall Survival and Progression-free Survival

mOS FOLFIRINOX 11.1 months
mOS Gemcitabine 6.8 months

RR FOLFIRINOX 31.6%
RR Gemcitabine 9.4%

mPFS FOLFIRINOX 6.4 months
mPFS Gemcitabine 3.3 months
Most Common Grade 3 or 4 Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>FOLFIRINOX (N = 171)</th>
<th>Gemcitabine (N = 171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>75/164 (45.7)</td>
<td>35/167 (21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9/166 (5.4)</td>
<td>2/169 (1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15/165 (9.1)</td>
<td>6/168 (3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anemia</td>
<td>13/166 (7.8)</td>
<td>10/168 (6.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39/165 (23.6)</td>
<td>30/169 (17.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24/166 (14.5)</td>
<td>14/169 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21/165 (12.7)</td>
<td>3/169 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>15/166 (9.0)</td>
<td>0/169</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated level of alanine aminotransferase</td>
<td>12/165 (7.3)</td>
<td>35/168 (20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>11/166 (6.6)</td>
<td>7/169 (4.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.
Quality of Life

Gourgou-Bourgade et al. JCO 2012
Desmoplastic Stroma in PDAC thought to contribute to drug resistance

\( Nab \)-Paclitaxel = nanoparticle albumin bound

Increases bio-availability of paclitaxel

Phase III MPACT study randomised 861 patients to gemcitabine alone or gemcitabine + nab-paclitaxel

\[\text{Gemcitabine + } Nab\text{-Paclitaxel}\]

Survival and Progression-free Survival

mOS Gem+ Nab–Paclitaxel 8.5
mOS Gem 6.7

RR Gem+ Nab–Paclitaxel 23%
RR Gem 7%

mPFS Gem+ Nab–Paclitaxel 5.5
mPFS Gem 3.7
Common Adverse Events of Grade 3 or Higher and Growth-Factor Use

<table>
<thead>
<tr>
<th>Event</th>
<th>nab-Paclitaxel plus Gemcitabine (N=421)</th>
<th>Gemcitabine Alone (N=402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event leading to death — no. (%)</td>
<td>18 (4)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Grade ≥3 hematologic adverse event — no./total no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>153/405 (38)</td>
<td>103/388 (27)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>124/405 (31)</td>
<td>63/388 (16)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52/405 (13)</td>
<td>36/388 (9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>53/405 (13)</td>
<td>48/388 (12)</td>
</tr>
<tr>
<td>Receipt of growth factors — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia — no. (%)‡</td>
<td>14 (3)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Grade ≥3 nonhematologic adverse event occurring in &gt;5% of patients — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>70 (17)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Peripheral neuropathy§</td>
<td>70 (17)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (6)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Grade ≥3 peripheral neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to onset — days</td>
<td>140</td>
<td>113</td>
</tr>
<tr>
<td>Median time to improvement by one grade — days</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Median time to improvement to grade ≤1 — days</td>
<td>29</td>
<td>NR</td>
</tr>
<tr>
<td>Use of nab-paclitaxel resumed — no./total no. (%)</td>
<td>31/70 (44)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* NA denotes not applicable, and NR not reached.
† Assessment of the event was made on the basis of laboratory values.
‡ Assessment of the event was made on the basis of investigator assessment of treatment-related adverse events.
§ Peripheral neuropathy was reported on the basis of groupings of preferred terms defined by standardized queries in the Medical Dictionary for Regulatory Activities.
FOLFIRINOX vs. Gem/nab-Paclitaxel

• No direct comparison

• Indirect comparison: slightly greater activity but worse toxicity with FOLFIRINOX

• NICE guidelines recommend offering FOLFIRINOX for patients with PS 0-1

• Pragmatically Gem-\textit{Nab}-Paclitaxel adopted by multiple studies as chemotherapy backbone
Suggested 1st line approach

Metastatic PDAC

Poor PS
- BSC
- Single Agent Gemcitabine

Good PS
- FOLFIRINOX
- Gem–Nab–Paclitaxel
- Gemcitabine combination

Clinical trial
Suitable for 50% patients

Nanoliposomal Irinotecan not NICE approved

Suggested 2nd Line Options

1st Line

2nd Line

3rd Line

Clinical Trials

FOLFIRINOX

Gemcitabine Based

Oxaliplatin Based

Gemcitabine Based

????

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Clinical Trials
Targeted Agents for Metastatic Disease
Gemcitabine + targeted agents

- Multiple attempts at combining gemcitabine with targeted agents
- Despite often promising pre-clinical data and early phase studies results resoundingly disappointing

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. Pts</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem + Cetuximab</td>
<td>745</td>
<td>3.4 vs. 3 (p=0.18)</td>
<td>6.3 vs. 5.9 (p=0.19)</td>
<td>Philip et al. (2010)</td>
</tr>
<tr>
<td>Gem + Bevacizumab</td>
<td>602</td>
<td>3.8 vs. 2.9 (p=0.18)</td>
<td>5.8 vs. 5.9 (p=0.95)</td>
<td>Kindler et al. (2010)</td>
</tr>
<tr>
<td>Gem + Aflibercept</td>
<td>546</td>
<td>3.1 vs. 3.7 (p=1.018)</td>
<td>6.5 vs. 7.8 (p=0.2034)</td>
<td>Rougier et al. (2013)</td>
</tr>
<tr>
<td>Gem + Axitinib</td>
<td>632</td>
<td>4.4 vs. 4.4 (p=0.5203)</td>
<td>8.5 vs. 8.3 (p=0.5436)</td>
<td>Kindler et al. (2011)</td>
</tr>
</tbody>
</table>
Gemcitabine + Erlotinib

- EGFR overexpressed in ~90% PDAC

- n= 569, Phase III, gem +/- erlotinib

- 1st agent to show statistically significant increase in mOS **BUT** Δ only 12 days for mOS

- **Skin rash** independent prognostic factor for disease control

- FDA and EMA approved **BUT** not in regular clinical use

Challenges of Targeted Treatment

- Complex mutational landscape
- Activating mutations of *KRAS* ubiquitous
- >50% inactivation *TP53*, *SMAD4* and *CDKN2A* BUT many infrequently mutated genes result in significant intertumoural heterogeneity
New Molecular Insights and Future Targets
Whole Genome Sequencing identified 4 Subtypes of PDAC

Actionable Genetic Alterations

- **Level 2B**: FDA-approved biomarker in another indication.
- **Level 3B**: Not FDA-approved biomarker or drug, but clinical evidence potentially links this biomarker or drug to response.
- **Level 4**: Not FDA-approved biomarker or drug, but preclinical evidence potentially links this biomarker or drug to response.

5.5% patients
- ERBB2 (6)
- CDK4 (2)
- BRCA 1/2 (8)
- BRAF V600E (1)
- Ros-1 (1)
- Alk (1)

4.6% patients
- AKT (1)
- ERBB2 (1)
- PIK3CA (5)
- FGFR1 amp (5)
- FGFR2 fus (1)
- NTRK3 fus (1)

68% patients

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Molecular Subtyping in Clinic: Immunotherapy

- Checkpoint inhibitor studies shown minimal to no activity in PDAC
- KEYNOTE-016 study of Pembrolizumab in patients with dMMR
- ~1% PDAC patients dMMR
- 5/6 PDAC patients responded

Molecular Subtyping in Clinic: PARP inhibitors

**Patients With Measurable Disease at Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n = 78)</th>
<th>Placebo (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response,* n (%)</td>
<td>18 (23.1)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Median duration of response, mos</td>
<td>24.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

**Median PFS, Mos**

- **Olaparib**: 7.4 mos
- **Placebo**: 3.8 mos

HR: 0.53 (95% CI: 0.35-0.82; \( P = .004 \))

Case Report

• 49 year old woman

• **2008**: Patient found to be a BRCA 1 mutation carrier, underwent prophylactic BSO and bilateral risk reducing mastectomy

• **Dec 2016**: Patient presented with new left upper quadrant pain

• **Jan 2017**: CT revealed 9.7cm pancreatic tail mass, 2cm liver metastasis and 9mm left lung lesion
Case Report

- **Jan 2017**: CT guided biopsy of pancreatic mass confirmed PDAC, baseline Ca19.9 889

- **Feb- May 2017**: Patient completed 8 cycles of FOLFIRINOX

- **July 2017**: Patient was randomized onto the POLO study of Olaparib maintenance following platinum chemotherapy for patients with germline mutations in BRCA 1/2
Disease Response

Feb 2017

June 2018

- Patient remained well on study and was able to go travelling with her family
- “I am back at work living a full life which is not dominated by this disease”
Case Report Continued

- **April 2019**: Patient developed progressive disease in lungs and pancreas and therefore came off study.

- **April 2019 - current**: Patient re-challenged with FOLFIRINOX chemotherapy and on recent CT scan there was resolution of the lung metastases and a reduction in the size of the primary disease.
Is research making a difference in PDAC?

- **YES!**

- Many challenges- inherent biological aggressiveness and heterogeneity of disease

- Modest improvements in chemotherapy combinations

- Targeted agents disappointing BUT new technologies improving understanding and providing novel targets

- Sound biological trial design with good early phase studies and predictive biomarker development key
Questions?