Treatment Approaches for Pancreatic Cancer: Hope on the Horizon

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Improvement in Outcomes: Metastatic Colon Cancer

Survival in Months


Survival in Months

BSC 5FU IFL FOLFOX FOLFIRI FOLFOX then FOLFIRI IFL plus Bev FOLFOX plus Bev FIRE-3 FOLFOXIRI plus Bev
Pancreatic Cancer Outcomes

Survival in Months

1996 2010 2015 2020

Gem or 5FU Gem Abrax FOLFIRINOX Gem Abrax then FOLFIRINOX

Von Hoff, NEJM, 2013, 369(18): 1691-1703
Outline

• Background
  – Pre-2011
  – A new era: Post-2011
  – 2nd & 3rd line therapy……

• Hope on the Horizon
  – Immunotherapy
  – Improved Local Therapy
  – Molecular Subtyping

• Increasing the Cure Rate
Pancreatic Cancer

- **US in 2012**
  - 43,920 new diagnoses
  - 37,390 deaths

- **Worldwide in 2008**
  - 278,684 new diagnoses
  - 266,669 deaths

- Will soon be the 2nd leading cause of cancer-related death

![Pancreas Diagram](image)
Pancreatic Cancer Statistics

- Pancreatic cancer can be a deadly disease
- At diagnosis
  - Only 20% are operable
  - 20% are inoperable, locally advanced
  - 60% are metastatic
- For the 10-20% who are operable
  - 80% will recur
  - 20% will be cured (<5% overall)
Metastatic Cancer: Pre-2011

• Gemcitabine
  – Very well tolerated
  – Initially approved based on an improved quality of life

• Survival benefit vs. 5-Fluorouracil
  – Average survival 5.7 months vs. 4.4 months
  – 1 year survival 18% vs. 2%

Gem vs. Gem + erlotinib – Phase III

- Average survival 6.37 months vs. 5.91 months
  - .46 months = 14 days
- 1 year survival 24% vs. 17%

New Standards – Post-2011

- FOLFIRINOX vs. Gemcitabine - Phase III
  - RR: 31% vs. 9%
  - Moderate toxicity

New Standards – Post-2011

• Gemcitabine + nab-paclitaxel vs. Gemcitabine
  – RR: 23% vs. 7%
  – Well tolerated

Von Hoff, NEJM, 2013, 369(18): 1691-1703
Sequential Treatment

- Induction Gemcitabine + \textit{nab}-paclitaxel
  - Up to 6 cycles
- Followed by FOLFIRINOX
  - Up to 6 cycles
- Median OS = 14.5 months
## Second Line Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trial design (N)</th>
<th>Schedule</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine (C) / Oxaliplatin (O)</td>
<td>Multicenter randomized phase II (190)</td>
<td>C 1000 mg/m² bid D1-14 (q 3 wks) O 130 mg/m² D1</td>
<td>PFS₃_months 51%</td>
<td>8.2 months</td>
</tr>
<tr>
<td>Cap/Gemcitabine (Gem)</td>
<td></td>
<td>C 825 mg/m² bid D1-14 (q 3 wks) Gem 1000 mg/m² D 1,8</td>
<td>PFS₃_months 64%</td>
<td>9.0 months</td>
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<tr>
<td>Gem/Ox</td>
<td></td>
<td>Gem 1000 mg/m² D1,8 (q 3 wks) Ox 130 mg/m² D8</td>
<td>PFS₃_months 60%</td>
<td>6.9 months</td>
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<tr>
<td>Cap/Ox</td>
<td>Phase II (41)</td>
<td>Cap 1000 mg/m² bid D1-14 (q 3 wks) Ox 130 mg/m² q 2 wks</td>
<td>9.9 wks</td>
<td>23 wks OS</td>
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<tr>
<td>Pemetrexed (P)</td>
<td>Multicenter Phase II (52)</td>
<td>P 100 mg/m² D q 3 weeks</td>
<td>NR</td>
<td>OS₃_months 75% Median OS 20 wks</td>
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<tr>
<td>Gem/Ox</td>
<td>Phase II (33)</td>
<td>Gem 1000 mg/m² D1 (q 2 wks) Ox 100 mg/m² D2</td>
<td>NR</td>
<td>6 months</td>
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<tr>
<td>Mitomycin (M) / Ifosfamide (Ifos)</td>
<td>Multicenter phase II (21)</td>
<td>M 8 mg/m² D1 (q 4 wks) Ifos 2,500 mg/m² D1-3</td>
<td>PFS₆_months 5%</td>
<td>3.7 months</td>
</tr>
<tr>
<td>Raltitrexed (R) / Ox</td>
<td>Phase II (31)</td>
<td>R 3 mg/m² (q 3 wks) Ox 130 mg/m²</td>
<td>PFS₆_months 14.6%</td>
<td>5.2%</td>
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<tr>
<td>Ox/5-FU</td>
<td>Phase II (30)</td>
<td>Ox 50 mg/m² (q 1 wk) 5-FU 500 mg/m²</td>
<td>NR</td>
<td>25 wks</td>
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<tr>
<td>Ox/Irinotecan (CPT)</td>
<td>Phase II (30)</td>
<td>Ox 60 mg/m² D1,15 (q 4 wks) CPT 60 mg/m² D1,8,15</td>
<td>NR</td>
<td>Median OS 5.1 months OS₁_year 23%</td>
</tr>
<tr>
<td>R</td>
<td>Randomized Phase II (38)</td>
<td>R 3 mg/m² D1 (q 3 weeks)</td>
<td>2.5 months</td>
<td>4.3 months</td>
</tr>
<tr>
<td>R/CPT</td>
<td></td>
<td>R 3 mg/m² D1 (q 3 wks) CPT 200 mg/m² D1</td>
<td>4 months</td>
<td>6 months</td>
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<tr>
<td>Paclitaxel (T)</td>
<td>Phase II (18)</td>
<td>T 73 mg/m² weekly</td>
<td>NR</td>
<td>17.5 wks</td>
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<td>S1/Cisplatin (Cis)</td>
<td>Phase II (11)</td>
<td>S1 20-30 mg bid D1-14 q 3 wks Cis 60 mg/m² D21</td>
<td>NR</td>
<td>81 days</td>
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<tr>
<td>5-FU/Irinotecan (FOLFIRI)</td>
<td>Phase II (50)</td>
<td>CPT 180 mg/m² D1 (q 2 wks) 5-FU bolus 400 mg/m² D1,2 5-FU infusion 600 mg/m² D1,2</td>
<td>3.2 months</td>
<td>5 months OS₇_months 32%</td>
</tr>
</tbody>
</table>

- Survival range 2-6 months
Second Line Therapy

- MM-398 = liposomally encapsulated irinotecan
- NAPOLI-1 Trial – multi-center Phase III
  - MM-398 vs. 5FU
  - 2nd line after gemcitabine-based therapy
- Overall survival benefit
  - 6.1 vs. 4.2 months (P=0.012, HR = 0.67)
Second Line Therapy

• Capecitabine +/- Ruxolitinib
  – OS: 4.3 months vs. 4.5 months

Hurwitz, et al, ASCO-2014
Second Line Therapy

- Capecitabine +/- Ruxolitinib
  - OS High CRP only: 1.9 vs. 2.8 months

*Hurwitz, et al, ASCO-2014*
New Hope on the Horizon

Novel Treatment Paradigms in Pancreatic Cancer
Immunotherapy
Immunotherapy and Pancreatic Cancer

• Inducing the immune system
• Vaccine Therapy
• GVAX + CRS-207 as $\geq 2^{nd}$ line therapy
  – GVAX – irradiated, GM-CSF-secreting allogeneic pancreatic cell lines → elicit antigenic response
  – CRS-207 - attenuated Listeria expressing mesothelin
• 90 patients
  – Median OS = 6.1 months

Le, JCO, 2014, 32(suppl 3; abstr 177)
Enhancing Anti-Tumor Immunity

• The programmed death 1 (PD-1) receptor is a negative regulator of T cells
• The PD-1 ligand (PD-L1) is expressed by tumor cells directly
• PD-1/PD-L1 inhibition → direct activation of cancer-specific T-cells

Boost immune recognition of the tumor – neoantigen release

- Combination with chemotherapy
- Combination with radiation
- Combination with a vaccine

Immunotherapy and Pancreatic Cancer

A Phase I/II trial of the anti-PD-L1 inhibitor, MEDI4736 in combination with PANVAC for patients with metastatic colorectal or pancreatic adenocarcinoma

- Metastatic colorectal or pancreatic cancer
- **Stable or responding on first line therapy**
  - “Maintenance” setting
- PS 0, 1
- Normal hepatorenal function
- Lead in Phase I - safety and tolerance
- Two parallel Phase II trials
- Treatment plan:
  - PANVAC prime and boost up to 5 months
  - MEDI4736 10mg/kg q2weeks up to 1 year

Monitoring and Evaluation
- Response assessment q8 weeks
Improved Local Therapy
Local Therapy for Metastatic Disease

- Will local therapy improve outcomes?
  - Surgical resection of hepatic metastases – no benefit to survival
  - 2-3 months off systemic chemotherapy

- Concurrent Local Therapy
  - Stereotactic radiation to the pancreas
    - Concurrent therapy is safe, and becoming standard
  - Liver-directed therapy
    - Chemo or radioembolization to the liver mets
      - TACE for pancreatic cancer – mOS = 16 months
      - TARE for pancreatic cancer – mOS = 22 months

Gurka, Radiat Oncol. 2013 Mar 1;8:44
Kim Alex, in preparation, 2014
A Phase II Trial of the Integration of Local Therapy for Patients with Metastatic Pancreatic Cancer

- Metastatic pancreatic adenocarcinoma - Receiving front line chemotherapy
- Systemic 5-FU-based chemotherapy
  - No evidence of progression after 6-8 weeks
  - Disease in the pancreas and liver
  - PS 0-2
  - Normal hepatorenal function
- Concurrent SBRT and transarterial radioembolization

10 endpoints = progression free survival
- Hypothesized PFS ≥ 10 months
- Historical comparison = 6.4 months

20 endpoints = RR, OS, AEs
Molecular Profiling
Precision Medicine

• Identify the right drug for each patient
  – Can we identify the:
    • 31% who respond to FOLFIRINOX
    • 22% who respond to Gem-abraxane

• Based on molecular characteristics
  – Next Gen Sequencing
  – Proteomics
  – Phosphoproteomics

• Are there molecular subgroups of patients:
  – 2% have HER2 overexpression
  – 3% have activating PIK3CA mutations
  – 3-5% have BRCA mutations
Patient “Tailored” Therapy

Predictive Markers

Gemcitabine
RRM1

Platinum
ERCC1

5-FU
TS

Tumor Biopsy

Low RRM1
Gem-Based

Low ERCC1
GemOX

High ERCC1
No Platinum

Low ERCC1
Gem 5FU

High TS
Gem Tax

Low TS
FOLFOX

High TS
Ox-Tax

Low TS
5-FU Tax

High TS Taxotere

High RRM1
No Gem

Low ERCC1
Platinum-Based

High ERCC1
No Platinum

Georgetown | Lombardi
Patient “Tailored” Therapy

• ESMO, 2013 – Hidalgo’s group
  – Molecular Profiling → Increased Survival
  – Retrospective Review
  – TS and TP were the strongest predictors
  – OS
    • Profiled patients = 12 months
    • Non-profiled patients = 7.6 months

• AACR, 2012 – Ramanathan’s group
  – Prospective study
  – Molecular Profiling → Therapy recommendations in 47 patients

Patient “Tailored” Therapy

- **Tumor biopsy**
  - Met Panc
  - 1st line therapy
  - PS 0-2

- **Physician’s Discretion**
  - 1st endpoint PFS – 5.5 vs. 9 months
  - 2nd endpoints
    - Overall survival
    - Response rate

- **Molecularly Tailored Therapy**

- **Tailored Therapy to Overcome Resistance Pathways**
  - **Second Line Therapy**

- **Systems biology**
  - Discovery of core resistance mechanisms

- **DNA exome Sequencing (TJU)**
- **Phosphoproteomics Analysis (GMU)**

- **Conditionally Reprogrammed Cancer cells**

- **RNA analysis (TJU): Transcriptome + Post-transcriptional**
Increasing the CURE Rate
Post-Operative Chemotherapy

• Clear benefit
  – Prolonged survival

• Examples
  – ESPAC-1 (5-Fluorouracil vs. observation)
    • Average survival: 20 vs. 15 months
    • % 5 year survival: 21 vs. 8%
  – CONKO-001 (Gemcitabine vs. observation)
    • Average survival: 22 vs. 20 months
    • % 5 year survival: 17 vs. 6%

Neoadjuvant Therapy

- For patients with resectable disease
  - Prior to surgery
  - Chemotherapy +/- radiation

- Are we just selecting patients out?
  - Overall survival still ~24 months
  - 30% of patients – surgery not appropriate
    - Patients become ill
    - Cancer grows/spreads before surgery
  - Of the remaining 70%
    - Improved overall survival
    - 30-34 months

- Highly debated topic
  - Should be pursued as a randomized trial
Can we apply metastatic regimens to localized disease

- Borderline resectable
  - Increase rate of resectability
  - Pre-op FOLFIRINOX or Gem + nab-paclitaxel
Metastatic $\rightarrow$ Earlier Stage

- Can we apply metastatic regimens to localized disease
  - Adjuvant/Neoadjuvant therapy
    - Increased eradication of micrometastatic disease
    - FOLFIRINOX or Gem + nab-paclitaxel
Thank You