Pancreatic cancer treatment approaches

Peter Hosein, MD

September 17th, 2015

Outline

- General principles of cancer
- Pancreatic cancer overview
- Advances in systemic therapy
- Management of locally advanced disease
- New approaches: Immunotherapy
- Case presentations
- Conclusion
Introduction to Oncology

- Treatment options fall into two main categories
  - **Local therapy:**
    - Surgery
    - Radiation
  - **Systemic therapy:**
    - Chemotherapy
    - Immune therapy

- Most cancers are treated with a combination approach e.g. surgery followed by chemotherapy and radiation
Introduction to Oncology

- **Goals of treatment should be clear from the start**
  - **Cure the cancer**
    - In general this applies to early stage cancers
    - Treatment is usually intensive and patients can get very sick from the treatment itself in an attempt to eradicate the cancer
  - **Improve length of life and quality of life**
    - Generally applies to advanced cancers or patients who are not in good shape for intensive treatment
    - Treatment is less intensive and may involve symptom control only

Introduction to Oncology

- **Cancer is a systemic disease**
  - Initial lesson from William Halsted and the radical mastectomy for breast cancer
  - After curative-intent resection, early and late metastases are frequent in most solid tumors

- Usual paradigm:
  - Localized disease → **Curative intent treatment**
    - Surgery ± radiation (prevent local relapse)
    - ± chemotherapy (prevent distant relapse)
  - Metastatic disease → **Palliative intent treatment** (usually chemotherapy)
Pancreatic Cancer: Challenges

- Stage for stage, pancreatic cancer is associated with the lowest survival rates of any major cancer type
- The vast majority of patients are inoperable at the time of diagnosis
- Pancreatic cancer is inherently resistant to most currently available therapies
- Many patients suffer from rapidly declining performance status, cachexia, pain and depression
- Compared with other cancer types, research funding for pancreatic cancer is disproportionately low given its mortality rate (fourth for cancer-related deaths in the US population)

Pancreatic Cancer Incidence and Mortality

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Female</th>
<th>Male</th>
<th>All Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>109,690</td>
<td>116,470</td>
<td>226,160</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,040</td>
<td>73,420</td>
<td>143,460</td>
</tr>
<tr>
<td>Bladder</td>
<td>47,130</td>
<td>55,680</td>
<td>102,810</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>43,210</td>
<td>44,250</td>
<td>87,460</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>32,000</td>
<td>40,250</td>
<td>72,250</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>31,070</td>
<td>36,180</td>
<td>67,240</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>24,520</td>
<td>26,040</td>
<td>50,560</td>
</tr>
<tr>
<td>Leukemia</td>
<td>22,280</td>
<td>28,630</td>
<td>50,910</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,930</td>
<td>22,980</td>
<td>44,910</td>
</tr>
<tr>
<td>All Sites</td>
<td>705,740</td>
<td>846,170</td>
<td>1,551,910</td>
</tr>
</tbody>
</table>

Pancreatic Cancer Incidence and Mortality

Patients Often Staged Clinically, Not by TNM

- Resectable (or operable) - No vascular involvement
- Borderline resectable - Moderate vascular involvement
- Locally advanced - Unresectable - Significant vascular involvement
- Metastatic

The Pancreas
## Definition of tumor-vessel interface

<table>
<thead>
<tr>
<th>Interface</th>
<th>R0 resection likely</th>
<th>R1 resection likely</th>
<th>R2 resection likely</th>
<th>Surgery/adjuvant tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/minor</td>
<td>likely</td>
<td>likely</td>
<td>likely</td>
<td>standard</td>
</tr>
<tr>
<td>Moderate</td>
<td>likely</td>
<td>suboptimal</td>
<td>likely</td>
<td>indicated</td>
</tr>
<tr>
<td>Major</td>
<td>likely</td>
<td>suboptimal</td>
<td>not indicated</td>
<td>indicated</td>
</tr>
<tr>
<td>Surgery</td>
<td>adjuvant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Resectable**
- **Borderline resectable**
- **Unresectable**

### Chemotherapy for advanced/metastatic pancreatic cancer
Gemcitabine for Metastatic Pancreatic Cancer

- Pivotal study defining role for gemcitabine as first-line treatment for patients with advanced pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>5-FU</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>5.6 m</td>
<td>4.4 m</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>Clinical Benefit*</td>
<td>24%</td>
<td>5%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Response Rate</td>
<td>5%</td>
<td>0%</td>
<td>NS</td>
</tr>
</tbody>
</table>

* A composite of pain (analgesic consumption and pain intensity), performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least 1 parameter without worsening in any others.

![Survival Time Graph](Image)

Phase III trials: Gemcitabine doublets vs Monotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Control Arm, Months</th>
<th>Study Arm, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gem vs Gem + cisplatin</td>
<td>192</td>
<td>6.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Gem vs Gem + oxaliplatin</td>
<td>313</td>
<td>7.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Gem vs Gem + 5-FU</td>
<td>322</td>
<td>5.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Gem vs Gem + capecitabine</td>
<td>533</td>
<td>6.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Gem vs Gem + pemetrexed</td>
<td>565</td>
<td>6.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Gem vs Gem + irinotecan</td>
<td>360</td>
<td>6.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Gem vs Gem + exatecan</td>
<td>349</td>
<td>6.2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

All negative trials

Phase III MPACT Trial: Gemcitabine ± nab-Paclitaxel

- Primary objective: OS
- Secondary endpoints: PFS, ORR, safety

Stratified by KPS, region, liver metastasis

Patients with metastatic pancreatic cancer, no previous treatment for metastatic disease, KPS ≥ 70, bilirubin ≤ ULN (N = 861)

- nab-Paclitaxel 125 mg/m$^2$ IV q3w + Gemcitabine 1000 mg/m$^2$ on Days 1, 8, 15 q4w (n = 431)
- Gemcitabine 1000 mg/m$^2$/wk for 7 wks, then on Days 1, 8, 15 q4w (n = 430)

Treat until PD


![Survival curve for nab-Paclitaxel and Gemcitabine](chart.png)
Pancreatic cancer resistance: the stroma

Immunohistochemical assay for collagen type 1 fibers in a gemcitabine-resistant human pancreatic cancer xenograft treated with nab-paclitaxel, gemcitabine, or gemcitabine plus nab-paclitaxel.

Phase III Trial of FOLFIRINOX vs Gemcitabine

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Stratified by ECOG PS (0 vs 1), center, tumor location (head vs other)

Gemcitabine (n = 171)
1000 mg/m² weekly x 7 of 8, then weekly x 3 of 4

FOLFIRINOX (n = 171)
Oxaliplatin 85 mg/
Leucovorin 400 mg/m²
Irinotecan 180 mg/m²
5-FU bolus 400 mg/m²,
5-FU CVI 2400 mg/m² over 46 hrs

Summary of chemotherapy

- There are two standard chemotherapy options for advanced pancreatic cancer:
  - FOLFIRINOX – usually used in younger patients who are in very good shape
  - Gemcitabine/nab-paclitaxel – well tolerated and effective even in frail patients
Approach to patients with locally advanced pancreatic cancer

Current algorithm for LAPC

- Patients with resectable disease after chemotherapy will be offered surgery
- Patients with unresectable but localized disease after chemotherapy will be offered chemoradiation
- Patients with unresectable but localized disease after chemoradiation will be offered IRE
- Patients with resectable disease after chemoradiation or IRE will be offered surgery
- Patients who undergo surgery will be offered adjuvant chemoradiation if radiation was not given before
FOLFIRINOX for LAPC – Dose intensity

Relationship between the number of full-dose cycles of neoadjuvant FOLFIRINOX and Survival

Ablation of LAPC with the Nanoknife™

Percutaneous Irreversible Electroporation for Downstaging and Control of Unresectable Pancreatic Adenocarcinoma

Govindarajan Narayanan, MD, Peter J. Hosein, MD, Geetika Arora, MD, Katuzka J. Barbery, MD, Tatiana Froud, MD, Alan S. Livingstone, MD, Dido Franceschi, MD, Caio M. Rocha Lima, MD, and Jose Yrizarry, MD

IRE (Nanoknife) example

62 year-old female with pancreatic adenocarcinoma and celiac axis encasement

Percutaneous placement of 4 probes around the tumor followed by delivery of an electric current between pairs or probes, leading to irreversible electroporation.
**Immune therapies for pancreatic cancer**

- GVAX Pancreas + CRS-207 vaccines
- Algenpantucel-L vaccine
- Immune checkpoint inhibitors
  - Ipilimumumab and Nivolumab
  - IDO inhibitors

**GVAX/CRS-207 vaccine**

- GVAX Pancreas: Irradiated, whole-cell tumor vaccine
  - Tumor antigens
  - GM-CSF

- GVAX Pancreas Dendritic Cell: Antigen uptake & Activation
  - T Cell Priming and Activation

- LADD Listeria: Live-attenuated *Listeria monocytogenes*
  - ∆actA
  - ∆inlB
  - Mesothelin
GVAX/CRS-207 early results

- Events/n: Cy/GVAX + CRS-207 34/45 (75.6%), Cy/GVAX 17/21 (81.0%)
- Median, months: 9.7 (95% CI 6.1 to 10.5) for Cy/GVAX + CRS-207, 4.6 (3.8 to 5.5) for Cy/GVAX
- P = 0.0167 (one-sided)
- P = 0.0395 (two-sided)
- HR, 0.5290

GVAX/CRS-207 ongoing study

- Metastatic pancreatic cancer
- FOLFIRINOX for 4-6 months
- Randomize
- Continue FOLFIRINOX
- Ipilimumab
- GVAX/CRS-207 Vaccine

This study is available at:
- Washington University (St. Louis)
- UCSF (San Francisco)
- Johns Hopkins (Baltimore)
9/17/2015

Hyperacute vaccine (Algenpantucel-L)

\[ \alpha(1,3)GT \text{ gene} \]

\[ \alpha(1,3)GT \text{ gene} \text{ introduced into} \]

\[ \alpha(1,3)GT \text{ gene} \text{ using viruses} \]

\[ \alpha(1,3)GT \text{ modified lung cancer cells} \]

\[ \alpha(1,3)GT \text{ modified pancreatic cancer cells} \]

• Persistent erythema and Induration 24-48 hrs. post injection.

• Skin biopsies of skin injection site shows significant cellular infiltration of various immune cells.
Algenpantucel-L ongoing study

Borderline resectable or unresectable pancreatic cancer

Chemo → Radiation → Surgery

Chemo → Radiation → Vaccine

Randomize

This study is available at UK

Other novel therapies

Growth factors
- HGF
- PDGF
- VEGF

Growth factors
- HGF
- PDGF
- VEGF

Chemosuppression
- Velpatasu
- Cisplatin

Chemosuppression
- Velpatasu
- Cisplatin

Cancer-associated Stromal

Cancer-associated Stromal

PESPI20
Disruption of matrix components through degradation to promote enhanced delivery of injected drugs

Disruption of matrix components through degradation to promote enhanced delivery of injected drugs

SMO inhibitors
- Sonidegib (OFEZOL)
- Vismodegib (ERI)

SMO inhibitors
- Sonidegib (OFEZOL)
- Vismodegib (ERI)

SIK pathway inhibitors
- Verizonin
- Ruplizumab

SIK pathway inhibitors
- Verizonin
- Ruplizumab

Cancer cell
- CSC
- SMO
- MDM2

Cancer cell
- CSC
- SMO
- MDM2

Vitamin D
- 1a,25 ODC
- 1a,25 ODC

Vitamin D
- 1a,25 ODC
- 1a,25 ODC

CXCR4 inhibitors
- Reslifivat (M2D1005)
- Vincristine
- Migalastat

CXCR4 inhibitors
- Reslifivat (M2D1005)
- Vincristine
- Migalastat

IDO inhibitors
- 1-MTP
- Indoleamine-2,3droxylase (IDO1)
- 1-MTP
- Indoleamine-2,3droxylase (IDO1)

IDO inhibitors
- 1-MTP
- Indoleamine-2,3droxylase (IDO1)
- 1-MTP
- Indoleamine-2,3droxylase (IDO1)

T-cell
- CAR
- T cell
- CAR
- T cell

T-cell
- CAR
- T cell
- CAR
- T cell

Tumour antigen presentation
- T cells
- Antigen presentation
- T cells
- Antigen presentation

Notch inhibitors
- Anti-DLL4 antibodies
- Dll4 (E701663, enflatin)
- Anti-Notch 2/3
- Anti-Notch 2/3
- Anti-Notch 2/3

Notch inhibitors
- Anti-DLL4 antibodies
- Dll4 (E701663, enflatin)
- Anti-Notch 2/3
- Anti-Notch 2/3
- Anti-Notch 2/3

MM-101
(animal stimulatory cytokine)

MM-101
(animal stimulatory cytokine)

Other novel therapies

Other novel therapies
Case presentation

- 46 year-old female
  - Presented with abdominal pain
  - CT scan showed a pancreatic tumor with no evidence of spread but the tumor was touching the superior mesenteric vein for a short segment
  - Endoscopy (endoscopic ultrasound - EUS) was performed
Case presentation

- Pancreatic cancer confirmed
- Tumor classified as “borderline resectable”
- Started chemotherapy with FOLFIRINOX
  - Received 8 cycles of chemotherapy (4 months)
- Then received radiation plus chemotherapy (6 weeks)
- Taken to surgery 7 months after diagnosis for Whipple resection

Overall result – no further evidence of cancer after intensive chemotherapy, radiation therapy and surgery
Conclusions

- Cancer is a systemic disease but can sometimes be cured with the correct sequence of treatments

- Chemotherapy options are improving in advanced pancreatic cancer (e.g. gemcitabine/nab-paclitaxel and FOLFIRINOX)

- Clinical trials are the way that we make advances. This is the best way to help yourself and others

Thank you!
Questions?