Treatment Approaches for Pancreatic Cancer

January 27, 2016

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Treatment Approaches in Pancreatic Cancer

Janet E. Murphy, MD MPH
Pancreatic Cancer Action Network Webinar
January 27, 2016

Disclosures

- Consulting, Merrimack Pharmaceuticals
Treatment Approaches in Advanced PDAC

- Chemotherapy
- Targeted therapy
- Immunotherapy

PanCan Clinical Trials Finder – An Amazing Resource… But Understanding the Trials is Daunting.
Objectives

- Provide a framework for understanding treatment strategies in this disease
- Review state-of-the-art treatments for the different stages of the disease
  - Advanced (Stage IV)
  - Locally advanced/borderline resectable
  - Upfront resectable
- Discussion

How Medical Oncologists Think About Pancreatic Cancer

*Can the cancer be taken out with a surgery?*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable (20%)</td>
<td>Metastatic (53%)</td>
</tr>
<tr>
<td>Borderline resectable</td>
<td>Locally Advanced</td>
</tr>
</tbody>
</table>
Can the cancer be taken out with a surgery?

**YES**
- Resectable
- Borderline resectable
- Locally Advanced

**NO**
- Advanced

- Chemotherapy
- Targeted Therapy
- Immunotherapy

Principles of **Chemotherapy**

- Since cancer, unlike infections, are “self” and not “other,” it is difficult to isolate and attack only the bad cells
- Chemotherapy targets rapidly dividing cells in the body
- The downside is the collateral damage – chemotherapy side effects
- The benefit is that strong, toxic therapy is delivered to pancreas cancer cells
- Major advances in the last 5 years
Dawn of a new era: FOLFIRINOX 2010

PRODIGE4/ACCORD11 study –

Combination chemotherapy:
5FU + Oxaliplatin + Irinotecan

VS

Gemcitabine

Criteria for enrollment:
• 75 years old or younger
• Very fit

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOLFIRINOX (N=178)</th>
<th>Gemcitabine (N=178)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (30.0)</td>
<td>16 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>66 (37.5)</td>
<td>71 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26 (14.6)</td>
<td>59 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>25 (14.4)</td>
<td>25 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Rate of objective response†</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>54 (31.6)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>24.5–39.1</td>
<td>5.4–14.3</td>
<td></td>
</tr>
<tr>
<td>Rate of disease control‡</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>120 (70.2)</td>
<td>87 (50.8)</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>62.7–76.9</td>
<td>43.1–58.6</td>
<td></td>
</tr>
<tr>
<td>Response duration — mo</td>
<td>5.9</td>
<td>3.9</td>
<td>0.57</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>4.8–7.1</td>
<td>3.1–7.1</td>
<td></td>
</tr>
</tbody>
</table>

* CI denotes confidence interval, and FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin.
† The rate of objective response was defined as the percentage of patients who had a complete response or partial response.
‡ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease.

Conroy et al NEJM May 2011

FOLFIRINOX prolongs survival among fit patients

Conroy et al NEJM May 2011
Dawn of a new era: Gemcitabine-Abraxane 2013

“MPACT” study - International

- 10% of patients were older than 75
- 7-8% of patients were less “fit”

Gemcitabine-paclitaxel improves survival too.

Von Hoff et al NEJM Oct 2013

Nal-irinotecan (MM 398) – new kid on the block

- Phase III study, in patients previously treated with gemcitabine based treatment

- Nal-iri + 5FU improved outcomes over 5FU alone

- *First second-line study showing survival benefit*

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An important benefit to our new choices

- Incremental addition of *multiple lines of therapy* leads to much, much better outcomes

- In pancreas cancer, *choice* of options can also lead to *SEQUENCING* of options.

- Common path in fit patients with metastatic disease:
  1) FOLFIRINOX
  2) Gem-Abraxane
  3) Clinical trial
Treatment Approaches in Advanced PDAC

- Chemotherapy
- Targeted therapy
- Immunotherapy

Targeted Therapy in Stage IV Lung Cancer

Targeted Therapy: The Pancreatic Cancer “Genome”

BRCA2 (inherited mutation) as target for therapy

Figure 2: Familial Pancreatic Cancer—All cases of pancreatic cancer, with proportionate delineation of genes known to comprise part of the familial subset, are shown. Data from: Hahn et al J Nutr Cancer Inst 2003;77; Lowenfels et al J Nutr Cancer Inst 1997;23; Rabois et al Am J Gastroenterol 2006;94; Sheldon et al Br J Cancer 1999;79; Couch et al Cancer Epidemiol Biomarkers Prev 2007;6; McWilliams et al Eur J Hum Genet 2011;6; Witt et al Nat Genet 2000;52; Ritterhouse et al J Gastrointest Surg 2011;6; McWilliams et al Cancer 2010;64.

Schrader et al
Oncology 2012
Targeting the Tumor Microenvironment

Angiogenesis inhibitors
Collagen inhibitors
Hyaluronic Acid inhibitors

Treatment Approaches in Advanced PDAC

• Chemotherapy
• Targeted therapy
• Immunotherapy
Immunotherapy: Vaccines

Randomized Phase II study at Johns Hopkins:

Patients randomized to GVAX alone versus combination with Listeria vaccine, CRS-207.

The two vaccine combination doubled the survival time of a small group of patients with advanced pancreatic cancer.

First positive study that suggests immune therapy has a potential ROLE in pancreas cancer!

Immunotherapy: Checkpoint Inhibitors

- Anti-CTLA-4
- Anti-PD-1
- Anti-PD-L1

Tested as single agents and in combination in pancreas cancer in ongoing trials
Immunotherapy

Adoptive T Cell Transfer

1. T cells are removed from patient
2. Genetic modification of T cells
3. Patient receives modified T cells
4. Enhanced immune response

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Clinical Trials in Advanced Disease – let’s classify

70 trials match your criteria

- Diagnosis: Adenocarcinoma - Stage IV, Diagnosed at Stage IV
- Treatment History: None

[List of clinical trials]

- Phase I Study of SU-5416, a PI3K Inhibitor, in Combination With N-palmitoylated Beremulin in Advanced Cancer Patients
- Phase I Trial of Hypoxia-Activated Radiosensitizer in Combination With MEK/ERK Inhibitors For Patients With Metastatic Melanoma And Lung, Breast And Pancreatic Cancers
- Phase II Study of Pazopanib and N-palmitoylated (Abraxane) in Metastatic Pancreatic Adenocarcinome
- Phase II Study of Pembrolizumab and N-palmitoylated (Abraxane) in Metastatic Pancreatic Adenocarcinome
- Phase II Study of the CD40 Agonistic Monoclonal Antibody APH-44M
- Phase I Trial of the ABG-12-101 Treatment With Sorafenib/Novo, Paclitaxel/Novo, Chemotherapy in Pancreatic Cancer
- Phase I Study of Tocilizumab in Patients With Advanced Solid Tumors
Clinical Trials in Advanced Disease – let’s classify

Can the cancer be taken out with a surgery?

**YES**
Resectable

**Borderline resectable**

**Locally Advanced**

**NO**
Metastatic

Figure 10: Pancreatic Tumor—Computed tomography (CT) scans show involvement of the pancreatic head (red arrow) and invasion of the superior mesenteric artery (yellow arrow) by tumor.

Image courtesy of [Massachusetts General Hospital](https://www.mgh.org/cancercenter)
Superior Response Rates of both Gem-Abraxane and FOLFIRINOX

Table 1: Overall Survival, Progression-free Survival, and Response Rates in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>FoLFIRINOX (N=177)</th>
<th>Gemcitabine (N=177)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival — mo (95% CI)</td>
<td>4.2 (3.9-4.4)</td>
<td>3.7 (3.4-4.0)</td>
<td>0.80</td>
<td>(0.67-0.95)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Survival rate — % (95% CI)</td>
<td>67 (62-71)</td>
<td>55 (50-60)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>35 (31-39)</td>
<td>22 (18-27)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>26 (23-30)</td>
<td>9 (7-11)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>6.4 (6.0-6.8)</td>
<td>4.6 (4.1-5.1)</td>
<td>0.02</td>
<td></td>
<td></td>
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Table 2: Objective Responses in the Intention-to-Treat Population

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<td>68 (39.4)</td>
<td>71 (41.5)</td>
<td>0.70</td>
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<td>8 (4.6)</td>
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<td>Rate of objective response — %</td>
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<td>30 (17.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>No. (95% CI)</td>
<td>54 (31.6)</td>
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<td>Rate of disease control — %</td>
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"Neoadjuvant" FOLFIRINOX in Borderline disease

Preoperative FOLFIRINOX followed by CRT and surgery in borderline resectable PDAC (Alliance A021101)

**Treatment Schema**

- Real-time centralized review of all radiographic studies and enrollment criteria
- Prospective CC of all treatment modalities
Giving neoadjuvant chemotherapy – MGH Clinical Trial in patients with UPFRONT RESECTABLE disease

- Study of Neo-adjuvant RO7009789 Alone or Neo-adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine Followed by Adjuvant RO7009789 Plus Nab-Paclitaxel and Gemcitabine for Patients With Newly Diagnosed Resectable Pancreatic Carcinoma
- Phase I study of Intraoperative Radiation Therapy for Resectable Pancreas Cancer
- Phase I Dendritic Cell Vaccine and Chemotherapy for Patients With Pancreatic Cancer
- Phase I Study of the CD40 Agonistic Monoclonal Antibody APX005M
- Phase I Stereotactic Body Radiotherapy Dose Escalation in Pancreatic Cancer
- Phase I Study Gemcitabine, Nab-Paclitaxel, Radiation Therapy, Sorafenib, Vorinostat in Previously Untreated Pancreatic Cancer Patients
- Phase I Study of Nab-Paclitaxel Plus Gemcitabine with Concurrent MR-Guided IMRT in Locally Advanced Pancreatic Cancer
- Phase I Trial Using Single Dose PEGPH20 and Cetuximab in Pancreatic Adenocarcinoma Prior To Surgical Resection
- Phase I Pilot Trial of Neoadjuvant Paricalcitol to Target the Microenvironment in Resectable Pancreatic Cancer
- Phase I Pilot Study Using Neoadjuvant FOLFIRINOX and Stereotactic Body Radiotherapy (SBRT) Followed by Surgery in Borderline Resectable Pancreatic Cancer
**Conclusion: Current Clinical Trials**

- **YES**
  - Resectable
  - Borderline resectable
  - Locally Advanced
  - Neoadjuvant chemotherapy, radiation, targeted therapy, and immune therapy along with surgery to improve outcomes

- **NO**
  - Metastatic
  - Chemotherapy
  - Targeted Therapy
  - Immunotherapy
  - Combination Therapy

**Meeting PanCan’s Mission**

**VISION OF PROGRESS / $200 MILLION BY 2020**

**OUR VISION: DOUBLE PANCREATIC CANCER SURVIVAL BY 2020**

Of the major cancers, pancreatic cancer has the lowest survival rate.

In 2010, our organization declared a bold and aggressive vision: After seeing too little progress in pancreatic cancer survival in over half a century, the Pancreatic Cancer Action Network put a stake in the ground to double pancreatic cancer survival by 2020.

This is our Vision of Progress.
Thank you for your participation.

If you have questions, please contact our Patient Central at (877) 272-6226 or e-mail patientcentral@pancan.org.

www.pancan.org