Novel Treatment Approaches in Pancreatic Cancer

Janet E. Murphy, MD MPH
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Objectives

- Provide orientation to pancreas cancer
- Discuss the different stages of the disease
- Review state-of-the-art treatments, focusing on our approach for different stages of the disease
- A few words about immunotherapy
- Provide a personal viewpoint on this disease
- Question period
Background

Pancreatic Anatomy

The origins of invasive pancreas cancer
How Medical Oncologists Think About Pancreatic Cancer

Can the cancer be taken out with a surgery?

YES  NO
Resectable  Borderline  Locally  Metastatic
(20%)  resectable  Advanced  (53%)

Can the cancer be taken out with a surgery?

YES  NO
Resectable  Borderline  Locally  Metastatic
  resectable  Advanced
Combination chemotherapy: 5FU + Oxaliplatin + Irinotecan

VS

Gemcitabine

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

Conroy et al. NEJM May 2011

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

VonHoff et al. NEJM Oct 2013
### “FOLFIRINOX-Plus” Studies in Metastatic Disease

- **FOLFIRINOX-LDE 225** (inhibits the “smoothened” pathway, crucial for cancer stem cell maintenance, tissue repair, and proliferation)
- **FOLFIRINOX-IPI-926** (inhibits the hedgehog pathway, which interacts with the smoothened pathway)
- **FOLFIRINOX-PEGPh20** (hyaluronidase, which breaks down the thick rind around pancreas cancers to enhance drug delivery)
- **FOLFIRINOX followed by Immunotherapy**

### “Gem-abraxane-plus” studies in metastatic disease

- **M402 and ODSH** (heparin like molecules with anti-cancer properties)
- **PEGPh20** (hyaluronidase)
- **Vaniciumab and OMP-54F28** (antibodies against Wnt pathway, which allows cancer cell proliferation)
- **OMP-59R5** (antibody against Notch3 pathway, which allows cancer cell proliferation and blood vessel formation)
- **Dovitinib** (small molecule that binds FGFR3, which allows cancer cell proliferation and blood vessel formation)
“Gem-abraxane-plus” studies in metastatic disease

- Bevacizumab (Avastin – antibody which prevents blood vessel formation)
- PLX7486 (binds several tyrosine kinases which promote cell survival and proliferation)
- IDO inhibitor (blocks the IDO pathway, which suppresses the body’s immune system and is overactive in cancer)
- TH-302 (potent chemotherapy that is only activated in low-oxygen conditions like tumors with poor blood supply)

- LCL-161 (small molecule that inhibits anti-cell death proteins in cells to increase sensitivity to cell death with chemotherapy)
- Erlotinib (small molecule that binds to the epidermal growth factor receptor on cell surfaces)
- OGX-427 (inhibits production of Hsp27, a heat-shock protein which prevents cell death)
- Additional chemotherapies – capecitabine, cisplatin
An important benefit to our new choices

- Lesson from colon cancer: incremental addition of multiple lines of therapy extended average survival from six months to greater than two years.

- 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

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Can the cancer be taken out with a surgery?

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<tr>
<th>YES</th>
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Figure 10: Pancreatic Tumor—Computed tomography demonstrates involvement of the posterior wall of the superior mesenteric vein (green arrow) as well as near-total encasement of the superior mesenteric artery (yellow arrow). (c) 2021 Massachusetts General Hospital. All rights reserved. Image courtesy of Alex Bwais, MD.
Can we convert these cancers to resectable?

- Mainstay of treatment: chemotherapy – to prevent spread and sterilize “micrometastatic” disease.

- The holy grail of locally advanced disease – to get patients to an operation – the only curative treatment.

- Historical rates of conversion very low – less than 10% with gemcitabine chemotherapy.

- HOWEVER, FOLFIRINOX and Gem-Abraxane demonstrate significant response rates – far higher than gemcitabine alone.
MGH Experience So Far – FOLFIRINOX in LAPC

- 22 patients with LAPC
- 12/22 patients were taken to the operating room for exploration (most with radiation after chemo).
- 5/12 patients underwent R0 resections
- 7/12 patients had surgically unresectable disease, and six of these patients had intraoperative radiation therapy (IORT) administered
- Of the six undergoing IORT, only one patient has experienced progressive disease
- R0 resection rate of 23% (5 of 22 patients) may reflect a new era of converting locally advanced pancreatic cancer into resectable pancreatic cancer with the use of FOLFIRINOX.

Is there a role for radiation therapy in LAPC?

- Controversial!
- LAP-07 study – ASCO 2013
  - Patients randomized to 4 months of gemcitabine vs gemcitabine/erlotinib
  - Patients who did not have progression were further randomized to radiation therapy
  - No difference in progression-free and overall survival
  - What about quality of life? Pain reduction? Time off therapy?
Strategic additions to chemotherapy in LAPC

Goal: enhance chemotherapy delivery
- FOLFIRINOX Losartan (anti-hypertension drug which has the potential to decrease collagen production around the tumor)
- FOLFIRINOX-PEGPh20 (hyaluronidase)

Goal: Decrease inflammation and enhance immune response
- FOLFIRINOX-PF-04136309 (inhibits inflammation response, proliferation, metastasis)
- FOLFIRINOX or Gem/Abraxane + Algenpantucel-L (vaccine which enhances body’s immunity against cancer)

Summary: What can we hope for in patients with unresectable disease?
- In a small but growing subset, we can convert to “resectable”
- Experimental therapies hope to enhance these odds
- Role of radiation is controversial but, to my view, beneficial
- Potential for durable responses even if surgery is not on the table
- Ultimately, considered by most to be on the spectrum of metastatic disease
Can the cancer be taken out with a surgery?

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

- **NO**
  - Metastatic

Approaches to the upfront resectable patient

Current standard: Surgery followed by gemcitabine chemotherapy

- **Resected pancreatic cancer**
- **Randomization** (stratified by R, T, N)
  - Gemcitabine for 6 months
  - Observation for 6 months
- **Follow-up every 8 weeks**

Gemcitabine after surgery improves:
  - Disease-free survival
  - Overall survival

**CONKO-001 Study**
Does radiation enhance the chance of cure?

- Controversial! No definitive study to prove it does.
- RTOG 0848 Study underway

Gemcitabine x 5 months → 1 more cycle chemo → Chemoradiation

Improving on this standard

- Giving stronger “adjuvant” chemotherapy
- Giving “neoadjuvant” chemotherapy
- Adding experimental drugs
- Any of the above, with radiation
### Giving stronger “adjuvant” chemotherapy

- ESPAC-4 trial in Europe: adjuvant gemcitabine vs gemcitabine + capecitabine
- Multiple US studies of adjuvant gemcitabine vs gem-abraxane
- Adjuvant FOLFIRINOX
- Adjuvant FOLFOX-Avastin
- Adjuvant Gemcitabine + pancreas cancer vaccine (GVAX)

### Giving “neoadjuvant” chemotherapy

- Neoadjuvant Gem-Abraxane → Surgery
- Neoadjuvant FOLFIRINOX → Surgery
- Neoadjuvant Gem-Abraxane → Radiation → Surgery
- Neoadjuvant FOLFIRINOX → Radiation → Surgery
Adding experimental drugs

• Neoadjuvant Gem-Abraxane-LDE225 (Smoothened pathway inhibitor)

• Neoadjuvant Gem-Abraxane-Hydroxychloroquine (anti-malaria drug with anti-cancer properties)

• Neoadjuvant Hydroxychloroquine + Proton beam radiation (Mass General)

Immunotherapy

• Pancreas cancer evades the immune system.
• Cells secrete chemicals that actively steer immune cells away from the tumor
• This provides a strong rationale for the development of immune therapy in this disease.

1) Vaccines
2) “Checkpoint inhibitors”
Immune therapy - Vaccines

- How do vaccines work?
- GVAX (previously mentioned in "adjuvant" trial setting)
  - Improving on GVAX – how do we rev up the immune system even more?
  - 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!

GVAX + CRS 207

3-arm randomized ECLIPSE trial:
- GVAX + CRS 207
- GVAX alone
- Chemotherapy alone

- Target population: previously treated pancreas cancer patients.
Immune therapy – Checkpoint inhibitors

- Anti-CTLA4
- Anti-PD1
- Anti-PDL1

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

Dana-Farber Harvard Cancer Center Clinical Trials

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