Pancreatic Cancer: Medical Therapeutic Approaches

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Pancreatic cancer is the hardest cancer of all to treat

Pancreatic cancer: Why so difficult to treat?

1) Hard to diagnose / discovered in advanced form

2) Drugs not as effective as desired

3) Lack of sophisticated/integrated multidisciplinary care

4) Patients a little older, sometimes hard to use intensive treatments

5) PESSIMISM
Pancreatic cancer: Goals of therapy

- Quality of life
- Quantity of life
- A chance for a cure

Challenge Goal: Double 5-year survival by 2020
Pancreatic cancer: Pyramid of success

Early detection
Better drugs
Multidisciplinary teams
Supportive care
Optimism

Optimism
A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.

--Winston Churchill

www.gavatorta.com
Pancreatic cancer:
Key supportive care issues

- Pain
- Depression
- Diabetes
- Weight loss
- Nausea/vomiting, stomach dysfunction (GOO)
- Biliary obstruction/infection
- Bleeding/bloodclots
- Other medical problems
Pancreatic cancer: Initial evaluation

Any patient with any combination of…

1) abdominal pain
2) weight loss
3) jaundice
4) new- onset diabetes, or
5) acute pancreatitis,…

think pancreas cancer!!!
Pancreatic cancer:  
Keys to diagnosis

1. High “index of awareness”
2. Remember key risks
3. Multiple key clinical features
4. Early sophisticated imaging
5. Repetitive testing

You don’t have pancreatic cancer **unless** a biopsy proves you do
Pancreatic cancer: Standard evaluation

- History and Physical Examination
- CBC/diff/plt/chemistry panel
- CA19.9
- Chest imaging
- CT scan of abdomen using special imaging techniques for pancreas detail
Pancreatic cancer: Basic categories

Pancreatic cancer

Localized

Is it RESECTABLE ????

Metastatic

Cure as many people as possible!

Turn into a chronic disease
Complete resection of pancreatic cancer is usually necessary, but usually not sufficient for a permanent cure

Pancreatic Cancer: Clinical Stages

• Localized- initially resectable 15%
• Localized- not initially resectable 35%
• Metastatic-50%
Pancreatic Cancer: FDA Approved Treatments

Metastatic pancreatic cancer: Options for treatment

1. Supportive care (especially if function limited)

2. Chemotherapy - fluoropyrimidine-based (e.g. FOLFIRINOX) or gemcitabine-based (e.g. gemcitabine/nab-paclitaxel)

3. Clinical trial
Pancreatic cancer:
Commonly used drugs - 2014

- GEMCITABINE
- 5-FU
- Erlotinib
- Capecitabine
- Cisplatin
- Oxaliplatin
- Irinotecan
- Docetaxel
- Nab-Paclitaxel

What is better than gemcitabine ??
Folfirinox vs. gemcitabine
(Conroy et al. NEJM 2011)

- 342 patients, randomized phase III
- Response rate nearly 3x higher than gemcitabine
- Time to progression 2x higher than gemcitabine
  (p<.00001)
- Overall survival 50% longer than gemcitabine
- But.......... 
- Harder, more expensive to use, side effects greater
Gem/nab-paclitaxel in metastatic pancreatic cancer
(von Hoff. NEJM 2013)

• 861 patients, randomized phase III
• Response rate more than 3x higher than gemcitabine
• Time to progression ~50% longer than gemcitabine
• Overall survival ~ 1/3 longer than gemcitabine
• Easier to take than FOLFIRINOX for most patients
You need an experienced surgeon!

Pancreatic cancer: Surgical volume and outcome
(Birkmeyer NEJM 2002)

<table>
<thead>
<tr>
<th># cases / year</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>16.2%</td>
</tr>
<tr>
<td>1-2</td>
<td>14.4%</td>
</tr>
<tr>
<td>3-5</td>
<td>10.9%</td>
</tr>
<tr>
<td>&gt;16</td>
<td>3.9%</td>
</tr>
</tbody>
</table>
However, surgery alone cures pancreatic cancer only 10% of the time!

Therefore, even when pancreatic cancer is removed or localized, since it has usually already spread (about 90% of the time) (i.e. a systemic disease), systemic therapy (i.e. drugs) should be given....

...but how best??
Pancreatic cancer: Treatment of resected disease

- **Observation** – probably not a good option for patients willing able to take therapy

- **Chemotherapy only** - gemcitabine or 5FU/LV for 6 months is the standard of care

- **Chemotherapy / XRT** - patients with high risk of local recurrence, good in experienced centers

- **Clinical trial**
Pancreatic cancer: Treatment of locally advanced disease

- Supportive care
- Chemotherapy only
- Chemotherapy / XRT
- Clinical trial
  - but, different expectations than in resectable disease
Pancreatic cancer: Types of clinical trials

- Phase I  Safety
- Phase II  Effect (does it work?)
- Phase III  Efficacy (is it better?)
- Phase IV  Effectiveness (does it work in a community practice?)

Patient and Liaison Services (PALS)

- disease & treatment information
- clinical trials search
- specialized info search
- support resources

Pancreatic cancer education packet (mailed within 24 hours)

matched back with original PALS Associate
Clinical Trial Database

- All Phase I,II,III pancreatic cancer-specific clinical trials in U.S.
  - Does not include solid tumor trials
- Verified and updated on an ongoing basis (monthly)
  - Clinicaltrials.gov & institutional websites
  - Direct interaction with trial investigators
  - Membership on national cancer committees
- 2,400 clinical trial searches in 2013

Pancreatic cancer: Major treatment aims

1) Better systemic agents
2) Better integration of therapies
3) Personalized treatment
Pancreas cancer: The future of treatment

1st line

- Patient preference
- Tumor biology

2nd line

- Patient comorbidity
- Economic limits

3rd line

Pancreatic cancer: Types of new drugs

- Chemotherapy
- Anti-stem-cell therapy
- Anti-stromal therapy
- Immunotherapy
- Targeted therapy
A PARP- inhibitor (olaparib) in pancreatic cancer
(Kauffman et.al. PROC ASCO 2013)

- 23 patients multiple prior therapies
- All with BRCA 1 or 2 mutations
- 5/23 (22%) response 13/22 (57%) disease control
- Side effects tolerable
- Over 40% lived an additional year or more

Cancer stem cells are resistant to standard therapies

(from Nature. 2001;414:105-11.)
CTGF in pancreatic cancer
FG-3019 trial: Results
(Picozzi et.al. GI Oncology Symposium- 2013)

• 75 patients
• No toxicity from FG-3019
• Overall amplifies survival by ~ 50%
• Can predict response by measuring CTGF and FG-3019 drug levels
• In best patients, drug combination as effective as FOLFIRINOX

FG-3019 in locally advanced, non-downstageable pancreatic cancer

Gemcitabine + nab-paclitaxel +/- FG 3019 x 24 weeks

↓

Surgery
Key Attributes of *Listeria monocytogenes* for Being an Effective Vaccine Vector

- Two key attributes for inducing robust innate and adaptive immunity
  - Naturally targets dendritic cells
  - Intracellular localization

- Permit re-administration to boost existing immune responses

- Practical Considerations
  - Ease and cost of manufacturing
  - Thermostable formulation

- Acceptable safety profile
  - Live-attenuated *Listeria ΔactA/ΔinlB*
  - KBMA *Listeria*
GVAX with and without CRS-207 in advanced pancreatic cancer
(Le et al., Proc ASCO 2013)

- 93 patients
- Virtually all patients had previously progressed despite at least 1 prior type of chemotherapy
- Side effects tolerable
- GVAX/CRS-207 combination improved survival by ~50% over vaccination only

Radiolabelled antibodies as targeted therapy (Clivatuzumab)

Pancreatic cancer: Integrated multidisciplinary care

Pancreatic cancer: Issues in resectable disease

1. Radiation
2. Better chemotherapy
3. Neoadjuvant therapy
4. Better radiotherapy
5. Immunotherapy
Pancreatic cancer—potential advantages neoadjuvant therapy

1. Earlier systemic treatment
2. Better patient tolerance of drugs
3. More reliable delivery of drugs to cancer
4. Greater chance of removing all of tumor at surgery

Pancreatic cancer: Adjuvant therapy
RTOG 0848

resected pancreas cancer

- gemcitabine
- gemcitabine + erlotinib
- gemcitabine + XRT/5-FU
- gemcitabine + erlotinib + XRT/5-FU
Pancreatic cancer; Adjuvant therapy
APACT trial

- Surgery
- Gemcitabine
- Gemcitabine + Nab-paclitaxel

Virginia Mason Protocol

- XRT
- IFN
- CDDP
- 5-FU
Radiation field design
Standard vs. ACOSOG

Virginia Mason Protocol:
Actual long-term survival

(Picozzi et al. DDW 2009)

- Overall survival
- Disease-free survival

Cumulative Survival

Time after Surgery (years)

Median OS = 44 mo
Two-years = 56%
Five-years = 44%
6. Immunotherapy

Algenpantucel-L

Vaccination therapy following pancreatic cancer resection

Resected pancreatic cancer

Standard adjuvant therapy + pancreatic cancer vaccine

Standard adjuvant therapy
Preinvasive pancreatic cancer

Resectable pancreatic cancer

Non-resectable pancreatic cancer

Borderline resectable or “downstageable”

Non-resectable

Non-downstageable
Borderline resectable pancreatic cancer
Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses

- Comprehensive analysis of 24 pancreatic cancers
- Sequences of 23,219 transcripts, representing 20,661 protein-coding genes
- Average 63 genetic alterations, majority are point mutations


Theranostics Reverse Phase Array Process

Step 1: Sample Collection
- Cells freshly in a blind sample

Step 2: Laser Capture Microdissection
- (optional)

Step 3: Cell Lysate Generation

Step 4: Multiple Protein Lysates
- are printed on replicate slides with positive controls and calibrator standards

Step 5: Antibody Staining
- Each slide undergoes a specific immunohistochemical analysis with an appropriate antibody (via sequential or simultaneous methods)
Pancreatic cancer:
Seena -1 trial

Gemcitabine/nab-paclitaxel

Folfiri

Metformin + maintenance therapy based on molecular profiling

Pancreas cancer:
The future of treatment

Endodiagnostic (re)staging:
Fusion Radiology

Precancer  Cancer

Personalized drug therapy

Advanced Surgery  Novel CRT
Pancreas cancer: 2014

• OPTIMISM!!!
  • Better drugs
  • Improved multidisciplinary care
  • Earlier diagnosis
  • Personalized treatment strategies with reduced therapeutic toxicity

“The future ain’t what it used to be.”
  —Yogi Berra
THANK YOU!!!!