Treatment Approaches to Pancreas Cancer

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What am I going to do?

• First, give you some background language
• Second, define the stages as we discuss them
• Third, go stage by stage defining treatment options going backwards from most advanced to least advanced
  – Within these I will define the treatments, their side effects
What else?

• Every time I switch topics I will post a gratuitous photo of one of my pets

Nietszche
Disclosures

- I have a lot of clinical trials and I give advice to a lot of companies. I won’t list them all.
- Key to know that I have given advice to Celgene, the makers of nab-paclitaxel (Abraxane) and have been paid for that work.

Background

CHANCE
Some important background

- Of all the common cancers, pancreas cancer remains the most deadly with the lowest percentage of patients living 5 years or more
- That is starting to change
- So, scary it is, there is hope and the numbers from the past may already be changing

How did it change?

- Thanks to you, other pancreas cancer survivors, their families, friends and the Pancreatic Cancer Action Network:
  - There is more funding than ever going towards pancreas cancer research
  - The Recalcitrant Cancers Act has passed and pancreas cancer and Ras are now 2 of the 3 top priorities of the National Cancer Institute
**Key Point**

- Numbers are based on statistics and large groups.
- They cannot be used to predict anything specifically for an individual.
  - Definition of individual means everybody is unique.
- When doctors give a number, it is usually based on averages but a doctor cannot “give” a person x amount of time.

**Some language**

- **Standard of care**
  - Something that is used commonly.
  - FDA standards are usually the same, but some standards used by your doctors have not been brought to the FDA for approval.
- **Staging**
  - Two forms: AJCC (I-IV with some letters in between). We don’t use these most of the time.
  - Real life.
Real Life Staging

- Metastatic disease
  - This is stage IV only
  - Means disease has spread to a distant site
    - Can be an organ like the liver or lung
    - Can also be a lymph node that is too far from the pancreas to be considered localized

- Localized disease
  - No evidence the tumor has spread on our x-rays
  - 3 sub-types

Localized Disease

- Resectable (not a real word)
  - Appears by CT scan or MRI that it can be cut out by a surgeon
    - Note: Surgeons have varying skills so there can be a bit of variation as to what they think they can cut out

- Borderline resectable
  - A major blood vessel appears to be too involved for immediate surgery but with treatment and shrinkage this could change

- Locally Advanced, Unresectable
  - Major involvement of the blood vessel and it is extremely unlikely even with shrinkage that it can ever be removed
Clinical Trials

- The most important hope for the future
  - Should be considered every time treatment plan is going to change
  - To learn more about trials in your area, contact the PALS program
    - pals@pancan.org
- Protocols are not always trials
  - Sometimes they are the way a practice treats a certain situation
  - More commonly called pathways now

Guidelines

- Guidelines are being created a lot now
- These are suggestions about best practices based on the literature
- Two main ones in the US: ASCO and NCCN
  - ASCO: Focus on limited areas one at a time, will not comment much if there is no data
  - NCCN: The most commonly used guidelines worldwide use expert opinion when there is no data
Layla

Note: the blankets were not arranged in her best interests and she opted to toss the pillows off the bed

Treatment of Metastatic Disease

• Because the tumor has spread beyond the ability to cut it out with a knife, the focus is on systemic therapy
  – Systemic therapy is treatment that gets all around the body
  – Types are:
    • Chemotherapy
    • Targeted therapy
    • Immune therapy
Gemcitabine single Agent
Background

- Gemcitabine (Gemzar, 2',2'-difluorodeoxycytidine)-originally developed as an antiviral
  - Too toxic for this
  - Had activity against cancer cell lines in the lab
- Tested as a single agent in 2nd line and as first line (treatment after 5-FU)
  - Few responses but
  - Doctors noted that patients claimed they felt better without tumor response
    - Note: response in a clinical trial is a lot of shrinkage. Mild shrinkage counts as stable disease

Gemcitabine vs. 5FU

- Gemcitabine beat 5-FU
  - Median survival (most important but not the primary endpoint of the study)
  - 1-year survival
  - Clinical benefit response (almost 5 times better than 5-FU)
  - Note: We now know that 5FU was not given in the most effective manner

Burris, JCO 15:2403, 1997
Side effects of Gemcitabine

- Immediate
  - Nausea/vomiting
  - Fatigue
  - Flu-like symptoms
  - Irritation to the vein
  - Rash
  - Shortness of Breath

- Delayed
  - Hair loss
  - Lower blood counts
  - High liver blood tests
  - Rash
  - Edema (swelling)

- Rare
  - HUS/TTP
  - Interstitial pneumonitis
  - Can bring back effects of radiation

A lot of drugs have been compared to gemcitabine

```
RANDOMIZE

Gemcitabine Alone
Other Drug = 5-FU
  lots of things that ended in TECAN
  Everything we found that blocked VEGF
  A bunch of things that ended in nib and mab

None of these beat gemcitabine. Some nearly tied it, but this ain’t horseshoes
```
What has combined with gemcitabine?

- Drugs that didn’t work
  - Bevacizumab
  - Cetuximab
  - Sorafenib
  - Axitinib
  - Irinotecan
  - Sunitinib
  - Many others

- Drugs that bordered on working
  - Cisplatin
  - Oxaliplatin
  - 5FU
  - Capecitabine

Drugs that combined with gemcitabine and won

- Erlotinib
  - Hazard ratio = 0.81

- Nab-paclitaxel
  - Hazard ratio = 0.72

- What is a hazard ratio?
  - Compares curves to curves rather than time point to time point
  - 0.72 means there is a 28% better chance at any time of being alive on gemcitabine + nab-paclitaxel compared to gemcitabine alone
FOLFIRINOX

- This is actually 4 drugs, 3 of which are chemo
  - FOLinic acid—like folic acid
  - 5-FU
  - IRINotecan
  - Oxaliplatin

- Showed a lot of promise in a phase II so the study was continued to phase III

FOLFIRINOX: Survival Curve

- Med Survival: 11.1 vs 6.8 months
- Stratified Log-rank test, p<0.0001
- HR=0.57 : 95%CI [0.45-0.73]
Important Note

• Sometimes two drugs combine well and sometimes they don’t
  – Gemcitabine + oxaliplatin is not better than gemcitabine alone
  – 5-FU + oxaliplatin is better than 5-FU alone
  – Similar story for irinotecan

Are there trade-offs with these two new regimens?
Grading side effects

- Grade 1 = mild
- Grade 2 = moderate
- Grade 3 = Serious
- Grade 4 = life-threatening

- However, if it is happening every day, grade 2 can be very limiting:
  - E.g. grade 2 fatigue: not relieved by rest, interferes with activity


<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>nab-P + Gem n = 421</th>
<th>Gem n = 402</th>
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</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE leading to death, %</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Grade ≥ 3 hematologic AEs, %</td>
<td></td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>38</td>
<td>27</td>
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<tr>
<td>Leukopenia</td>
<td>31</td>
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<td>9</td>
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<td>Anemia</td>
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<td>Patients who received growth factors, %</td>
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<td>15</td>
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<tr>
<td>Fever neutropenia, %</td>
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<td>1</td>
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<tr>
<td>Grade ≥ 3 nonhematologic AEs in &gt; 5% of patients, %</td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>7</td>
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<tr>
<td>Peripheral neuropathy, c</td>
<td>17</td>
<td>&lt; 1</td>
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<tr>
<td>Diarrhea</td>
<td>6</td>
<td>1</td>
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</tbody>
</table>

Grade ≥ 3 neuropathy

| Time to onset in days, median          | 140                 | 113         |
| Time to improvement by ≥ 1 grade in days, median | 21                  | 29          |
| Time to improvement to grade ≤ 1 in days, median | --                 | --          |
| Patients who resumed nab-P, %         | 44                  | --          |

a Based on lab values. b Based on investigator assessment of treatment-related events. c Grouped term. nab-P, nab-Paclitaxel; Gem, gemcitabine; AE, adverse event.
FOLFIRINOX: hematological AEs

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th>Gemcitabine N=169</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
<td>All</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79.9</td>
<td>45.7</td>
<td>54.8</td>
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<tr>
<td>Febrile Neutropenia</td>
<td>7.2</td>
<td>5.4</td>
<td>2.4</td>
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<tr>
<td>Anemia</td>
<td>90.4</td>
<td>7.8</td>
<td>94.6</td>
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<tr>
<td>Thrombocytopenia</td>
<td>75.2</td>
<td>9.1</td>
<td>54.8</td>
</tr>
</tbody>
</table>

42.5% of the pts received G-CSF in the F arm vs 5.3% in the G arm.
One toxic death occurred in each arm.

AE, adverse event


FOLFIRINOX: main non-hematological AEs

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<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
<td>All</td>
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<tr>
<td>Infection without neutropenia</td>
<td>6</td>
<td>1.2</td>
<td>7.1</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>70.5</td>
<td>9</td>
<td>0.6</td>
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<tr>
<td>Vomiting</td>
<td>61.4</td>
<td>14.5</td>
<td>43.2</td>
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<tr>
<td>Fatigue</td>
<td>87.3</td>
<td>23.2</td>
<td>78.7</td>
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<tr>
<td>Diarrhea</td>
<td>73.3</td>
<td>12.7</td>
<td>30.8</td>
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<tr>
<td>Alopecia (grade 2)</td>
<td>32.5</td>
<td>(11.4)</td>
<td>3.0</td>
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<tr>
<td>ALT</td>
<td>64.8</td>
<td>7.3</td>
<td>83.8</td>
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Comparing gemcitabine + nab-paclitaxel to FOLFIRINOX

- Gemcitabine + nab-paclitaxel
  - Hazard ratio and median not as good as FOLFIRINOX
  - Some say side effects less than FOLFIRINOX
  - Studied around the globe, including Eastern Europe
  - Allowed slightly less healthy patients

- FOLFIRINOX
  - Numbness/tingling goes away more slowly than gemcitabine + nab-paclitaxel
  - Studied only in France
  - Restricted age to <75 years old

Comparing key side effects

<table>
<thead>
<tr>
<th></th>
<th>nab-pacli + GEM</th>
<th>FOLFIRINOX</th>
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</thead>
<tbody>
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<td>Fatigue</td>
<td>17</td>
<td>23.6</td>
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<tr>
<td>Diarrhea</td>
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<td>12.7</td>
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<tr>
<td>Neuropathy</td>
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<td>9</td>
</tr>
<tr>
<td>Neutropenia</td>
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<td>45.7</td>
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<tr>
<td>Neutropenic fever</td>
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<td>5.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Neuropathy appears to resolve faster with nab-paclitaxel

Von Hoff, et al GI ASCO 2013 and ASCO 2013
Which one is best?

- We don’t know for certain
  - There are reasons to use each
- FOLFIRINOX has been modified which may reduce side effects (unlikely to reduce effectiveness)
- FOLFIRINOX has not been tested in people over 75 years old

One last note

- Performance status
  - The ability of a person to conduct the activities of life
    - Karnofsky 0-100%, 100% is normal
    - ECOG: 0-4, 0 is normal
    - ECOG 1 = 90 and 80% on Karnofsky
    - ECOG 2 = 60 and 70% on Karnofsky
  - FOLFIRINOX has only been tested in ECOG 0-1
  - Gemcitabine + nab-paclitaxel was tested in Karnofsky 70-100%
My doctor is using something other than what you mentioned

- Many doctors use a regimen that they have had good experiences with
  - They are neither right nor wrong
  - Everybody is trying to do their best for their patients
  - These regimens are just not proven in large trials to be better or worse than gemcitabine alone
  - But small trials or individual experiences can be tricky and sometimes misleading
    - That is why other docs might not be using your doctor’s favorite regimen

Bisket
Locally Advanced, Unresectable

- A lot less is known here
  - We have official definitions, but to some extent we are not entirely sure who is convertible to surgery and who isn’t
  - Options include: chemotherapy and radiation
    - FOLFIRINOX and gemcitabine + nab-paclitaxel have not been studied here yet
  - Early studies all combined chemotherapy + radiation together, called chemoradiation

One key study: LAP-07

- Randomization of chemotherapy (gemcitabine or gemcitabine + erlotinib) to chemotherapy followed by chemoradiation
- No difference in survival between arms
- However, control of disease in the area of the pancreas was better with radiation
- Current question is whether or not chemoradiation would have done better with better chemo
Other things being done

• Stereotactic radiation
  – Highly focused, intense radiation to a small area
    • Names include SBRT, gamma knife, cyberknife, proton beam
    • None are absolutely proven.
    • Differences are subtle

• Surgery on the SMA
  – If this goes wrong, and it does, the side effects can be horrible

They are not friends
**Borderline Resectable Disease**

- Goal here is to try to improve the likelihood the surgeon can remove the whole tumor with negative margins
  - R0: no tumor at any of the cut edges of the pathology specimen
- Chemotherapy and chemoradiation have both been used
- No randomized trials

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**Borderline Resectable**

- No standard of care
- Trial preferred
- Most common these days, based on intergroup trial is:
  - Chemo first
  - Followed by chemoradiation
  - Followed by surgery
Resectable Disease

- Head of pancreas (80%)
  - Whipple is most common
  - Pylorus preserving pancreaticoduodenectomy
    - Variation on Whipple
- Body, tail (20%)
  - Partial pancreatectomy
  - Distal pancreatectomy
    - Spleen usually has to come out with this one
Early Detection

• Even when we catch this disease early, surgery alone only cures 10-12% of people
  – Chemotherapy, either gemcitabine or 5FU, improves this
  – The US has used chemoradiation also, but this is not proven to be better
• Current study randomly assigning people who have had resection to chemo alone or chemo followed by chemoradiation

CONKO-001 Kaplan Meier Disease Free Survival
CONKO-001 Kaplan Meier
Survival

Chemotherapy with gemcitabine
53% patients censored (+)
Observation
45% patients censored (+)

ESPAC 3: Gemcitabine vs 5FU

Median S(t) = 23.0 months (95% CI: 21.1, 25.0)
Median S(t) = 23.6 months (95% CI: 21.4, 26.4)

χ² LR = 0.74, p = 0.39, HR GEM vs 5FU/FA = 0.94 (95% CI: 0.81, 1.08)
R1 Resection

• While it looked like everything was removed, when the pathologist looked at it under the microscope
  – Microscopic cells came right up to the edge where the knife cut
• Almost every trial has shown this group also benefits from chemotherapy
• Similarly, this group may benefit from chemoradiation more than R0

CONKO-001 Disease Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy median (months)</th>
<th>Observation median (months)</th>
<th>P – value (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19.3</td>
<td>11.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>13.1</td>
<td>7.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>R</td>
<td>14.0</td>
<td>7.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>R1</td>
<td>14.5</td>
<td>5.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>
Resectable Disease

- Standard of care is surgery first
- Chemotherapy with either gemcitabine or 5FU
- Clinical trials are focusing on 3 areas
  - New regimens:
    - APACT compares gemcitabine + nab-paclitaxel to gemcitabine alone
    - French are looking at modified FOLFIRINOX
  - Giving chemo or chemoradiation before surgery
  - Looking at the value of post-surgery radiation

Before You fall completely asleep
Other therapies

- Targeted agents
  - Still looking for ones that work in pancreas
  - Trying to target Ras mutations

- Immune therapies
  - Vaccines are in trials (GVAX is furthest ahead)
  - Immune modulators: free the immune system to attack—also in trials

Special situations

- BRCA mutations, PALB2 mutations, Fanconi anemia
  - Inherited in most cases
  - May be more susceptible to:
    - Platinums
    - Mitomycin
    - PARP inhibitors (experimental)
Palliative Care

- Never forget this whether we are giving anticancer therapy or not
  - Making a person feel better can make them live longer
    - Pain control has been shown to extend the life of people with pancreas cancer
    - Timely initiation of hospice has been shown to extend the life of people with pancreas cancer
- SYMPTOMS MATTER!!!

Last Thing

- There are a lot of myths out there
  - PET scan is better than CT:
    - No, it is just different. Different scans are needed in different situations
  - If you turn your body alkaline, you will kill the cancer
    - Your pH is 7.4. You can make your urine alkaline, but unless your kidneys have failed you can't turn you alkaline. Your body can't survive in a more alkaline environment either
  - Chemotherapy kills the immune system
    - It reduces the neutrophil counts for short periods which can increase the risk of bacterial infections. The rest of the immune system is intact
Happy Father’s Day

Vanderbilt-Ingram Cancer Center