The Beast with an Achilles Heel: The Unique Vulnerability of BRCA Related Pancreatic Cancer

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<tr>
<th>Company</th>
<th>Relationship</th>
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<td>Eli Lilly Oncology</td>
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<td>TesaroBio</td>
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<td>Bristol-Myers Squibb</td>
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Outline

- Pancreatic cancer: a primer
- The relevance of BRCA mutations to pancreatic cancer
- Exciting science:
  - Changes for inoperable (incurable) patients
  - Changes for operable (curable) patients
  - Screening studies
- Beyond BRCA...
But first... a story...

Timing is Everything

- In 2012, SM was diagnosed with operable pancreatic cancer

- Chemotherapy side effects were accumulating... he was fatigued, had mouth sores, anemia, worsening nerve damage, chronic diarrhea

- Fortunately, in early 2014, a novel study of rucaparib (a PARP inhibitor) for BRCA-related pancreatic cancer had opened...
Pancreatic Cancer: A Primer
Pancreatic Cancer: A Primer

- 10-15% are operable (curable) at diagnosis

- For those with locally advanced disease, there is hope for resection in some cases, with chemotherapy and radiation prior to surgery to shrink the tumor

- For those with metastatic disease, treatment is ongoing chemotherapy
Pancreatic Cancer: A Primer

2001
Gemcitabine

No active chemotherapy options
Survival 3-5 months

2011
FOLFIRINOX

Survival 6-12 months

2013
Gemcitabine/Nab-Paclitaxel

2016
5-FU/Onivyde

WHAT ABOUT BRCA??

1Heinemann, 2001
2Conroy, 2011
3Von Hoff, 2013
4Wang-Gilliam, 2016
BRCA-Related Pancreatic Cancer

- Based on various studies, 3-15% of persons with pancreatic cancer have an inherited mutation in BRCA1 or BRCA2
- Biologically different!
- Importantly:
  - Responses to specific chemotherapies are enhanced
  - Survival tends to be longer (IF treated correctly...stay tuned!)
  - There are targeted drugs in active development
Which Pancreatic Cancer Patients Should be Tested for *BRCA* Mutation?

- Rarely, a patient with pancreatic cancer already has a diagnosis of *BRCA* mutation.

- Historically, we have done germline testing if:
  1. the patient is particularly young
  2. the patient has a prior history of other cancers
  3. the patient has a strong family history of cancers
  4. the patient is Ashkenazi Jewish

- Recent literature: You will miss many using this strategy\(^1\)

\(^1\)Hu, 2018
Which Pancreatic Cancer Patients Should be Tested for BRCA Mutation?

- Ongoing studies in which any patient with pancreatic cancer are tested: MSKCC and University of Pennsylvania
  - A brief video during the visit
  - Saliva or blood sample
  - Results released by: genetic counselor (Penn) or primary oncologist (MSKCC)

- Should this be standard care? Probably.
Why Does BRCA Matter?

Platinum → WT BRCA → BRCA MUT → X

Diagram showing DNA strand alterations due to BRCA mutations and platinum treatment.
Why Does BRCA Matter?

- FOLFIRINOX
- FOLFOX
- Cisplatin/Gemcitabine
- Gemcitabine/Oxaliplatin
- Capecitabine/Oxaliplatin

All commonly used and should be preferentially used in a BRCA mutation carrier
Full Cohort

Patients Who Received Platinum

Patients Who Did Not Receive Platinum

Reiss et al, JCO Precision Oncology, 2018
A New Problem...

- Patients with pancreatic cancer and BRCA mutations do exceptionally well with platinum therapy
- Over time, toxicity accumulates and therapy becomes progressively more challenging
- There is no standard of care alternative at this time
  - Dose reductions
  - Chemo “holidays”
  - Dropping particular agents...

Now what?
PARP Inhibitors

- Is there another way to exploit the “broken” machinery?
- Olaparib (Lynparza): Approved in breast and ovarian cancer
- Rucaparib (Rucabra): Approved in ovarian cancer
- Niraparib (Zejula): Approved in ovarian cancer
- Talozaparib: In development
- Veliparib: The weakest PARPi
Synthetic Lethality

Platinum → WT BRCA → BRCA MUT

Random Events → X

PARP Inh → PARP

Smiley face
An Important Caveat

- It has been shown that once a tumor is resistant to platinum therapy, it has a high likelihood of also being resistant to PARP inhibitors.

- It is key to use PARP inhibitors before resistance occurs.

- Schroff et al, JCO Precision Oncology, 2018
  - 15 platinum-resistant patients: 4 SD, 11 PD
  - 4 platinum-sensitive patients: 1 CR, 2 PR, 1 SD
PARP Inhibitors + Chemotherapy

- MSKCC (Eileen O’Reilly, MD)
  - (1) BRCA Mutation
  - (2) Metastatic PDAC
  - Cisplatin + Gemcitabine
  - Cisplatin + Gemcitabine + veliparib

- Georgetown (Michael Pishvaian, MD)
  - (1) BRCA Mutation
  - (2) Metastatic PDAC
  - mFOLFOX + veliparib
PARP Inhibitors as Maintenance

- Cumulative toxicity of chemotherapy can reduce a person’s quality of life dramatically
  - Neuropathy
  - Fatigue
  - Immune system suppression
  - Anemia
  - Hearing loss
  - Kidney problems

- What about using PARP inhibitors to maintain control?
POLO

- Ongoing/enrolling nationally; sponsored by AstraZeneca
- Will likely have results in 2019

(1) BRCA Mutation
(2) Metastatic PDAC
(3) Stable on platinum for ≥4 months

- Olaparib
- Placebo
RUCAPANC2

(1) BRCA or PALB2 Mutation
(2) Inoperable or Metastatic PDAC
(3) Stable on platinum for ≥4 months

- Ongoing/enrolling at University of Pennsylvania

Rucaparib
Future Directions for Incurable Patients

- Additional characterization of resistance mechanisms
- Combinations of PARP inhibitors with other “DNA repair prevention” drugs such as ATR inhibitors, WEE1 inhibitors, ATM inhibitors
- Combinations with other agents – immunotherapy is coming...
New Science for Curable Patients

- Most BRCA experts will choose a platinum-based regimen for patients who have a BRCA mutation and have undergone surgery to remove the tumor.

- First choice: FOLFIRINOX (Ox = Oxaliplatin)\(^1\)

- Other options:
  - FOLFOX (5-FU/Leucovorin/Oxaliplatin)
  - Gemcitabine/Oxaliplatin
  - Capecitabine/Oxaliplatin
  - Cisplatin/Gemcitabine

\(^1\)Conroy, ASCO 2018
New Science for Curable Patients

- Would adding a PARP inhibitor after chemotherapy improve survival even further?
- A national study to answer this question is in development

Stay tuned...!
New Prevention Strategies

- At this time, there is no proven screening test for pancreatic cancer
- For those at higher than average risk of pancreatic cancer, establishing an effective screening test is of enormous interest
What is the Risk of Pancreatic Cancer in BRCA Carriers?

- Lifetime risk in BRCA1 carriers is up to 5%
- Lifetime risk in BRCA2 carriers is up to 10%

Liede et al, JCO, 2004
Screening for Pancreatic Cancer

- No validated study
- CAPS5 (Dr. Michael Goggins)
  - 2,500 patients
  - IV secretin (0.2mcg/kg) at the time of EUS to induce pancreatic juice secretion
  - Pancreatic juice and circulating pancreatic epithelial cells (from blood) are analyzed for early markers of cancer development

- Open at: Yale University, Johns Hopkins, Dana Farber, University of Michigan, Columbia University, Case Western, University of Pennsylvania and University of Pittsburgh
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| Familial pancreas cancer                 | 1. >55yo  
2. 2+ family members with pancreatic cancer  
3. At least 1 relative is first-degree |
| Germline mutation carrier Group 1        | 1. >50yo or 10 years younger than age of onset of youngest relative with pancreatic cancer  
2. Confirmed carrier of FAMMM, BRCA2, PALB2 mutation |
| Germline mutation carrier Group 2        | 1. >55yo or 10 years younger than age of onset of youngest relative with pancreatic cancer  
2. Carrier of BRCA1, ATM or Lynch Syndrome  
3. At least one family member with pancreatic cancer |
| Hereditary pancreatitis                  | 1. Confirmed gene mutation that disposes to chronic pancreatitis  
2. ≥50yo |
| Peutz-Jeghers Syndrome                   | 1. ≥30yo  
2. At least 2 of 3 criteria of PJS or  
3. Confirmed STK11 carrier |
Screening via a Blood Test

- Dr. Ken Zaret recently published that plasma thrombospondin-2 (THBS2), when combined with regular CA 19-9 could:
  - Accurately exclude cancer in someone without it (98% specificity)
  - Correctly identify someone with stage I or II pancreatic cancer (87% sensitivity)
- Trials will be developed – keep an eye out
Beyond *BRCA*...

- *BRCA* mutations might not be the only ones that we can target with these strategies
- Other mutations in the DNA repair system may also be sensitive to the same strategies
  - *PALB2, CHEK2, ATM, ATR, BRIP1* and others
- Take Home Point: Trials for these patients are also underway!
What Happened to SM?

- Surgery (6/2012)
- Chemotherapy (6/2012-11/2012)
- Recurrence (11/2012)
- FOLFIRINOX (11/2012-5/2014)
- 10/2014: Started rucaparib
- 3/2013: BRCA2 Mutation
- Remains on rucaparib (four years TOMORROW)
Thank you!

Questions?

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