Precision Medicine for Pancreatic Adenocarcinoma

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Facilitates accurate predictions of which treatment and prevention strategies for a particular disease will work in which groups of people.

- **Precision Medicine**: Takes into account individual variability in genes, environment, and lifestyle (individual characteristics) for each person.
  - Includes particular tumor characteristics
    - Milieu (Environment)
    - Mechanisms of Development

- **Personalized Medicine**: Look at a particular individual’s genetic makeup to determine therapy
  - Has been subsumed into ‘Precision Medicine’

Although thought of as a new concept, it is not
- Blood Type donors and recipients
- HLA typing
Pancreatic Adenocarcinoma

The need for Precision Therapeutics

Pancreatic Adenocarcinoma

Risk factors

- **Smoking**
  - Cessation

- **Intraductal papillary mucinous neoplasms (IPMNs)**
  - Screening, although data lacking on efficacy of this strategy in reducing the risk of death

- **Hereditary pancreatic cancer syndrome**
  - BRCA1/2 and PALB2 (Partner and Localizer of BRCA2)
    - BRCA2 is the most common hereditary cause based on its prevalence
  - HNPCC
    - Lifetime risk of 3-4%
  - FAP
    - RR of 3-4X
  - Family history
    - Risk increase with number of affected FDRs
      - 4-5 x RR 1 FDR
      - 6-7 x RR 2 FDR
      - 32 x RR 3FDR
    - Trend to worse prognosis as generations pass

- **Patients with IPMN’s and hereditary concerns are intensively followed by GI and Surgery**
At Diagnosis Is Pancreatic Cancer a Systemic Disease?

• 163 cases with histologically confirmed carcinoma of the head of the pancreas
Neoadjuvant Therapy

• Potential benefits

  – Occult micrometastatic disease may become visible, can save resection morbidity

  – Potential to decrease rate of positive margins

  – Deliver chemotherapy and/or radiation without delay (25-35% adjuvant delayed > 8 weeks)

  – Can be delivered without affecting perioperative mortality / morbidity

  – In vivo drug sensitivity

  – Surrogate Marker trials to speed up new therapeutics
• CA19-9 (sialylated Lewis blood group carbohydrate antigen CA19-9)
• Preoperative levels were available
  – in 1,106 of 1,165 patients with resected pancreatic adenocarcinoma
  – 437 of 461 patients undergoing exploration with/without additional bypass procedure
• CA19-9 was increased in 75.4% of cancer patients.

Preoperative CA19-9 serum levels and survival

Pre-to-postresection CA19-9 changes and survival
CA19-9 response to neoadjuvant therapy predicts OS

Autophagy is Programmed Cell Survival

Stress

Autophagy

Recycling Damaged Materials

Programmed Cell Survival

Apoptosis

Programmed Cell Death

LC3-II

Lysosome
Resectable or Borderline PDA

**UPCI 13-074: Randomized Trial**
Preoperative Gem/Abraxane +/- HCQ

**PG**
- Cycle 1:
  - gemcitabine (1000mg/m²)
  - nab-paclitaxel (125mg/m²)
  - D1, D8, D15

**PGH**
- Hydroxychloroquine (HCQ) 600mg BID
- D1, D8, D15

**Surgery**
- D70-84

**Notes:**
- Cycle 1:
  - gemcitabine (1000mg/m²)
  - nab-paclitaxel (125mg/m²)
- Cycle 2:
  - gemcitabine (1000mg/m²)
  - nab-paclitaxel (125mg/m²)
- (R01 CA160417-01A1)
HCQ Results in Decreased CA 19-9

* p = 0.01
HCQ Improves Histopathologic Response

The bar chart shows the percentage of patients with different histopathologic responses to HCQ treatment. The x-axis represents different stages (I, IIA, IIB, III), and the y-axis represents the percentage of patients. The chart compares two groups: PG and PGH.

- For stage I, the PG group has a higher percentage compared to the PGH group.
- For stage IIA, the PG group significantly outperforms the PGH group.
- For stage IIB, the percentage is relatively low for both groups.
- For stage III, the PGH group shows a higher percentage than the PG group.

Overall, the graph indicates that HCQ improves histopathologic response, particularly in stages I and IIA, with PG showing superior results in these stages.
Neoadjuvant trials

- 24 trials listed on the NCI Trials website as of 7/15/2017
  - Immunotherapy or combinations thereof
    - NCT02446093: Neoadjuvant GMCI (Gene Mediated Cytotoxic Immunotherapy) Plus mFOLFIRINOX and Chemoradiation for Non-Metastatic Pancreatic Adenocarcinoma
    - NCT01088789: Vaccine Therapy and Cyclophosphamide in Treating Patients with Pancreatic Cancer
    - NCT02930902: Pembrolizumab and Paricalcitol with or without Chemotherapy in Patients with Pancreatic Cancer That Can Be Removed by Surgery
    - NCT02588443: RO7009789 (CD40 AGONIST) with or without Nab-paclitaxel and Gemcitabine Hydrochloride before and after Surgery in Treating Patients with Newly Diagnosed Pancreatic Cancer That Can Be Removed by Surgery
  - Stromal Agents
    - NCT0248727: PEGPH20, Gemcitabine Hydrochloride, and Nab-Paclitaxel in Treating Patients with Borderline Resectable Pancreatic Cancer
    - NCT02210559: A Phase 1/2 Trial of Gemcitabine Plus Nab-paclitaxel With or Without FG-3019 as Neoadjuvant Chemotherapy in Pancreatic Cancer
  - Radiation
    - NCT02723331: Combination Chemotherapy and Stereotactic Body Radiation Therapy before Surgery Followed by Combination Chemotherapy in Treating Patients with Pancreatic Cancer That Can Be Removed by Surgery
  - Directed Therapies
Targeted Therapy


• Affects function of TGF-β pathway
  – 5 mutations associated with hereditary hemorrhagic telangiectasia
  – 60 mutations in SMAD4 found to cause juvenile polyposis syndrome
  – Loss is seen in 40-60% of pancreatic adenocarcinomas

• Loss associated with metastasis in pancreatic cancer, and poorer prognosis
  – Up to 30% of patients dies with locally destructive disease (<10 mets)
  – 66 patients on autopsy
    • 2/9 SMAD4 loss with zero mets
    • 5/11 (45%) SMAD4 loss with 1-10 mets
    • 33/46 (72%) SMAD4 loss with widely met disease
• Prospective study at 3 academic medical centers of consecutive, unselected, newly diagnosed PDAC patients Ambry Genetics CancerNext Panel (32 genes)

Germline genetic testing in unselected pancreatic ductal adenocarcinoma (PDAC) patients (Abstract 1501)- Peter and Brand et al. ASCO 2017

BRCA2
- Penetrance varies on pedigree
- 3-5 X increased RR
- Because of prevalence of BRCA2, most common cause of hereditary PC

BRCA1

PALP/B

Targeted Therapy: DNA Damage Repair

tumor cells
DNA damage

STOP

PARP

Olaparib

DEATH
Combined Platinum and PARP inhibition

presentation

post treatment AZD2281 (olaparib)
Case Summary AH 54 yo female

- **January 2011**
  - dx’d with triple neg breast adenoca
  - Neoadjuvant A/C f/b T, f/b modified right radical mastectomy
  - 4 negative sentinel nodes, f/b CW XRT
- **July 2012:**
  - weight loss, ascites: ovarian cancer resected stage IIIC
  - BRCA2 testing positive
  - Taxol/Carbo through December 2013
  - maintenance taxol April 2013-August 2013, stopped secondary to worsening abdominal pain
  - CT demonstrated a SMAD4 deleted pancreatic mass, bx : c/w pancreatic primary
  - CA19-9: 2271, CA125 and CEA normal
Case Summary AH 54 yo female

10/2013

1/2014

8/2014

Abraxane
5FU
Cisplatin

Every 2 weeks x 6 cycles

Mitomycin-C
Xeloda

5 months through 8/2014

SBRT 8/2014

CA19-9:

5400 1320 19
Case Summary AF:
A 35-year-old male presented with fatigue, diarrhea and jaundice.

- Referral for abdominal computed tomography (CT) revealed a 2.1 cm pancreatic head mass and confirmed as adenocarcinoma by EUS aspiration. Deemed borderline resectable.

- Treatment
  - neoadjuvant FOLFIRINOX then gemcitabine and nab-paclitaxel for lack of response
  - stereotactic body radiation therapy with 12 gray x 3 fractions (36Gy total).
  - robotic-assisted Whipple was performed. ypT3N1
  - At 11 months, CT imaging showed enlargement of retroperitoneal, left periaortic and retrocaval lymph nodes consistent with metastatic disease. CA 19-9 of 584.9 units/mL.
  - Abraxane/Gemcitabine
  - Foundations Medicine (Cambridge MA) revealed an exon 13 EML4-exon 20 ALK translocation
  - Crizotinib started with stability of CA19-9, but stopped due to hematological toxicity
  - Ceritinib started, excellent response but with eventual progression of disease.
  - Nivolumab added
  - Alectinib – SD then PD
  - New CNS disease, progression – resection of a brain met and laminectomy
  - Lorlatinib (due to circulating L1159M resistance mutation)
Case Summary
Mutations per tumor

- Mismatch-repair proficient colon cancers
- Mismatch-repair deficient colon cancers

Categories:
- Liquid Tumors
- Pediatric Tumors
- Sporadic Adult Solid Tumors
- Mutagen Associated tumors
- Mismatch repair tumors
Study Design

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=25)

Cohort B
Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

Objective Responses

<table>
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<tr>
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<th>MMR-deficient CRC</th>
<th>MMR-proficient CRC</th>
<th>MMR-deficient non-CRC</th>
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<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td>10</td>
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<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
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• 58 yo gentleman with unresectable cholangiocarcinoma failed all available chemotherapy
• Foundations testing revealed biallelic somatic loss of MLH1
• Pembrolizumab q 2 weeks, within 4 weeks his CA19-9 normalized and in 3 months NED, remains on Pembrolizumab
67 yo gentleman with metastatic PDAC

- FOLFIRINOX for 3 months, stable disease and toxicity
- Abraxane/gemcitabine x 11 months with good response for 9 months then widespread progression (liver/lung/carcinomatosis)
- MSI status by IHC/PCR (now screening all gastric/colon/pancreaticobiliary) demonstrated PMS2 loss.
- Pembrolizumab started 9/2015
Hyaluronan (HA)

- Naturally occurring, linear, megaDalton polysaccharide and major component of the tumor stroma\(^1\)
- HA accumulation increases tumor interstitial gel-fluid pressure, which in turn compresses blood vessels and compromises blood flow\(^2,3\)
- HA accumulation is associated with accelerated tumor growth and is an independent negative predictor of survival in PDA\(^4\)

PEGPH20 (pegvorhyaluronidase alfa)

- A PEGylated form of recombinant human hyaluronidase PH20, which degrades HA and remodels the tumor stroma

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Stromal change: Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA). Abstract 4008
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Stromal change: Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDA). Abstract 4008
CQ Modulates FAP Expression

Chemo + CQ

Chemo alone

Brown: FAP
Chloroquine and anti-PDL1 Enhances Survival in Orthotopic Murine PDA

[Graph showing changes in tumor growth and percent survival]
Autophagy and Checkpoint Inhibition

HCQ D-2

Arm A
Resectable or borderline resectable PDA

Arm B

D1 D8 D15 D22
Gemcitabine Abraxane Cycle 1

D1 D8 D15
Gemcitabine Abraxane Cycle 2

Avelumab every 2 weeks until 1 week prior to surgery

Continue HCQ BID until evening dose prior to surgery

Surgery No less than 2 or more than 6 weeks post chemotherapy
How to restore productive immunosurveillance in pancreatic carcinoma?

1. Release of cancer cell antigens
   - Chemotherapy, vaccines
   - Targeted therapies

2. Cancer antigen presentation
   - CD40 agonists
   - TLR agonists

3. Priming and activation
   - anti-CTLA-4
   - anti-PD-1/PD-L1
   - adoptive T cell therapy
   - cyclophosphamide

4. Trafficking of T cells to tumors

5. T cell infiltration into tumors

6. T cell recognition of cancer cells

7. T cell killing of cancer cells
   - anti-CTLA-4
   - anti-PD-1/PD-L1

adapted from *Immunity* 39:1 2013
Chemoimmunotherapy for the treatment of cancer

Tumor Cell

Chemotherapy

Antigen

Immunogenic Tumor cell Death

Nowak A et al, Cancer Res 2003
Obeid M et al, Nat Med 2007

"Licensed" APC

"Licensed" APC

CD8

CD28

B

Cytokines

CD40

Agonist anti-CD40 mAb

Sotomayor et al, Nat Med, 1999;
Diehl et al, Nat Med, 1999;
French et al, Nat Med, 1999
Schematic Overview of Targeted Agents

- **Vasculature**
  - EndoTag-1
  - Abraxane (?)

- **Stroma**
  - Hyaluronidase (PEGPH20)
  - FG3019 (CTGF Mab)
  - TGF beta modulators

- **Tumor**
  - Abraxane(pinocytosis)
  - KRAS
  - Cell cycle inhibitors
  - ATM
  - Her2
  - Phosphoinositol
  - IGFR
  - Mek/Erk
  - MTOR
  - Akt
  - Y90-hPAM40

- **Immune cells**
  - Hydroxychloroquine
  - GVAX
  - CRS207
  - PD1/PDL1
  - CTLA4