Immunotherapy for Pancreatic Cancer

June 13, 2016

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Kelly & Ryan Waters

6/14/2016
Inflammatory networks and T cell immunosurveillance in pancreatic cancer

Lauren J. Bayne
Thesis Advisor: Robert H. Vonderheide
Cell and Molecular Biology

Immunotherapy for patients with pancreatic cancer

Robert H. Vonderheide, MD, DPhil
Director, Penn Pancreatic Cancer Research Center
Hanna Wise Professor of Cancer Research
Abramson Cancer Center
Perelman School of Medicine
University of Pennsylvania

The cancer immunotherapy revolution

CTLA-4 antibody
PD-1 antibodies
CART19 T cells
Cancer Immunotherapy: the future is now

• Novel antibodies that ‘cut the brakes’ on the immune system

• Genetically reprogrammed immune cells that attack cancer upon re-infusion (“CAR” T cells)

• Genetically engineered viruses that shrink tumors by activating the immune system

• Many more experimental therapies….

Status of cancer immune therapy in 2016

• A subset of patients clinically respond
• Variety of effective approaches
• For patients in whom a response occurs, response can be quite durable
• Notable toxicities are immune-related, but these are usually manageable, reversible
• Encouraging early reports with combinations
But most patients -- especially those with pancreatic cancer -- do not as yet respond to current immune therapies.

Pancreatic Cancer
The clinical and biological challenges:

- Early detection is difficult
- Suboptimal response to standard therapies
- Main tumor mutation (Kras) is currently ‘undruggable’
- Hostile microenvironment in pancreatic cancer
Rethinking the problem

Pancreatic cancer is not the same as melanoma

- We can build on prior success, but we cannot just cut and paste and expect it will work

- We need – and are gaining – a deeper understanding of the underlying biology, especially the surrounding tumor stroma that restrains the immune system in pancreatic cancer

Immunobiology of pancreatic carcinoma

Mutant Kras
Loss of TS

Desmoplastic stroma

Gemcitabine
**Immunobiology of pancreatic carcinoma**

- Fibroblasts
- Macrophages
- B cells
- Extracellular matrix
- Immature myeloid cells
- Regulatory T cells

*But, minimal infiltration of effector T cells in the TME in most patients*

---

**T cell immune surveillance of cancer**

- T cell response
- Elimination
- Immunoediting
- Escape
- Resistance to immune therapy

- Host/tumor immune suppression
- Peripheral tolerance
- Escape
- Overcome with CTLA4 or PD-1 mAb, or both
CTLA-4 and PD-1/PD-L1 antibodies interrupt ligand binding and stop negative immune signaling
- Activate pre-existing dysfunctional or exhausted T cells

Clinical response to checkpoint blockade has been linked to:
- Burden of somatic missense mutations in the tumor
- Predicted load immune targets derived from these mutations ('neo epitopes')
- Extent of T cells in the tumor
- PD-L1 expression in the tumor
- Microsatellite instability (MSI high)

T cell immune surveillance of cancer

HOT
- T cell response
- Host/tumor immune suppression
- Peripheral tolerance
- Overcome with CTLA4 or PD-1 mAb, or both

COLD
- Host/tumor immune suppression
- No T cell response in tumor
- Immune privilege
- Overcome by vaccination AND block immune suppression
Converting cold tumors to hot tumors to establish responsiveness to checkpoint blockade

Genetically engineered Lab model of pancreas cancer

CD3 IHC

Response to CTLA4 mAb
PD-1 mAb

No response to CTLA4 mAb
PD-1 mAb

Convert to Hot

CD8 IHC

Treatment with gemcitabine, nab-paclitaxel, agonist CD40

PD-1, CTLA4, or both

No tumor response

Regression
Improved Survival
Cures

Winograd et al. Cancer Immunol Res, 2015; Byrne and Vonderheide, in press
Strategies to tip the balance of immunity

Turn on T cells

↓

Turn off negative factors

Immunity

No immunity

Options for immunotherapy in pancreatic cancer

Vaccine → No response

Checkpoint blockade → No response

Vaccine + Checkpoint blockade → Tumor regression?
The Opportunity of Combinations

Break the ceiling of what single or dual checkpoint blockade can achieve

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Block checkpoints beyond CTLA4, PD1</td>
<td>TIM3, LAG3, TIGIT, VISTA, IDO1, TGFβ1, CD73</td>
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<tr>
<td>Generate anti-tumor T cells</td>
<td>Cancer vaccines, RT, chemo, CAR T cells</td>
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<td>Alter the TME and stroma</td>
<td>CCR2i, BTKi, CSF1Ri, FAP CAR, Treg depl</td>
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<tr>
<td>Improve T cell traffic to tumors</td>
<td>CXCR4 inhibitors</td>
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<tr>
<td>Repair deficits in antigen presentation</td>
<td>CD40, TLR, CD47</td>
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<tr>
<td>Provide T cell agonists</td>
<td>OX40, CD137, IL-7, IL-15</td>
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The Challenge of Immune Combinations

- So many pathways and so many drugs
- Too few patients on clinical trials (national average 5%)
- Will there be diminishing marginal return, not to mention toxicity, if we use checkpoint inhibitors in triple or quadruple combinations?
- Can we afford it?
Critical need: 
*Immune profiling and immune personalized medicine*

- Need assays that go beyond PDL1 testing
- Comprehensive (DNA, RNA, protein, metabolism, etc)
- Mutational panel sequencing insufficient to reach the goal
- **Goal is to identify a biomarker for response to:**
  - Treat only those most likely to respond
  - Eliminate risk by not treating those who will not respond, and
  - Address financial toxicity by focusing on value for the money

SU2C-Lustgarten grant in pancreatic cancer immunotherapy

**National effort**
- Seven institutions:
  - Penn/Johns Hopkins/Oregon/UCSF/WashU/Cambridge/Stanford
- Next-generation immune therapies for pancreatic cancer

**Multiple clinical trials**
- GVAX/Listeria plus PD-1 antibody
- CD40 plus chemotherapy
- Chemotherapy plus BTK inhibitor
- CD47 antibody
- CXCR4 inhibitor
Novel immune combination: GVAX + Listeria + PD1

GVAX Pancreas
Whole-cell tumor vaccine

LADD Listeria
Live-attenuated Listeria monocytogenes

Nivolumab
Fully human IgG4 antibody against PD-1

A Randomized Phase 2 Study of GVAX Pancreas Vaccine (with Cyclophosphamide) and CRS-207 with or without Nivolumab in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma

Patients with metastatic pancreatic cancer; received 1 prior chemotherapy for metastatic disease

1:1 randomization

Arm A Vaccine + Anti-PD-1

Arm B Vaccine Alone

Cy/GVAX
CRS-207

Nivolumab

12 months follow-up

NCT02243371
Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory

Before treatment

After treatment

CD40 antibody immune therapy for pancreatic cancer

Primary Lesion

Liver Metastasis

Baseline

After Treatment

3.9 cm

7.6 cm

2.1 cm

Not seen
**CD40 as neoadjuvant therapy in pancreatic cancer**

Phase I study of preoperative RO7009789 +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma

Arm A: RO7009789 (n=10)
Arm B: Gem/Abrax then RO7009789 (n=10)

<table>
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<tr>
<th>Day</th>
<th>Dx</th>
<th>Resect</th>
<th>Gem/Abra + RO7009789 x 4 cycles</th>
<th>observe</th>
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<td>Tissue and blood biomarkers</td>
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Penn PI, Vonderheide
JH PI, Laheru
NCT02588443

**Using radiation together with immune therapy**

- Radiation given to one tumor can make other tumors elsewhere in the body regress
- This only occurs when radiation is given with immune therapy (checkpoint antibodies)
- Any cancer, including pancreas ca
- This effect occurs because of T cell activation
- Best results with a highly specialized, short course of radiation therapy or proton therapy

‘RadVax’ – combining radiation with immune therapy

Radiation plus PDL1/CTLA4
NCT02639026

Radiation plus PD1
NCT02303990
Phase I study of TERT DNA + IL-12 DNA vaccine

- Patients with pancreatic cancer in remission after surgery and adjuvant therapy
- TERT DNA + IL-12 DNA every 4 weeks x 4 into the muscle with electroporation (EP)
- EP device: Inovio’s CELLECTRA®-5P

Objectives
- Primary: safety
- Secondary: immune response

NCT02327468
Conclusions

• Research efforts in pancreatic cancer are accelerating

• New discoveries are driving novel therapies, especially immune therapies

• Clinical trials are critical

Thank you for your participation.

If you have questions, please contact Patient Central at (877) 272-6226 or e-mail patientcentral@pancan.org.

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