Immune Therapy for Pancreatic Cancer

December 16, 2014

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Immune therapy for pancreatic cancer

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December 16, 2014

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
What we know about pancreatic cancer

Scientific knowledge

Year

1990 2000 2014

Attendance at a national scientific meeting on pancreatic cancer

Number of Attendees

Year

2003 2014

<30 >450

1990 2000 2014

Scientific knowledge
Massive increase in the depth and breadth of research activity in pancreatic cancer

Scientific publications per year

Publications on breast cancer
- In 2012: 13,925
- In 2002: 5,090

We are here
Redesigned chemotherapy for pancreatic cancer

- Two new combinations of drugs for patients with metastatic disease
  - FOLFIRINOX (Conway et al, NEJM, 2011)
  - Gemcitabine/Abraxane (Von Hoff et al, NEJM, 2013)

- Rates of major tumor regression to initial therapy for metastatic disease have gone from <5% to 25%-30%, with better survival
  - But still not a ‘cure’

- Implications and next steps
  - It’s not just gemcitabine alone anymore
  - Provides a better initial approach to stabilize our patients so additional therapies, such as immune therapy, can be added
  - Chemotherapy does not ‘ruin’ the immune system

The challenge and opportunity of stroma
### Immune biology of pancreatic cancer

Bayne and Vonderheide, Curr Opin Immunol, 2013

![Diagram showing immune responses in pancreatic cancer](image)

### Cancer immunotherapy trials for patients with pancreatic cancer

<table>
<thead>
<tr>
<th>Treatment clinical trials for PDA *</th>
<th>2014</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open trials</td>
<td>372</td>
<td>385</td>
</tr>
<tr>
<td>Immunotherapy trials</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

**Percentage of all trials exploring immunotherapy for PDA**

- Same calculation in melanoma: 22.1% 17.0%
- Same calculation in breast cancer: 3.9% 1.0%

* Clinicaltrials.gov, assessed by RHV
Monoclonal antibodies can stimulate the immune system

Negative immune checkpoints: the ‘brakes’

Pardoll, Nat Rev Can, 2012
Negative immune checkpoints: the ‘brakes’

Pardoll, Nat Rev Can, 2012

PD-1 antibody with and without CTLA-4 antibody

Pembrolizumab for patients with metastatic melanoma
Hamid et al, NEJM, 2013

Nivolumab plus ipilimumab for patients with metastatic melanoma
Wolchok et al, NEJM, 2013
Results so far using antibodies against negative immune checkpoints in patients with pancreatic cancer

- Single agent αPD-L1 – no responses (Brahmer et al., *NEJM*, 2012)
Strategies to tip the balance of immunity

- Turn on T cells
- Turn off negative factors

Immunity
No immunity

IMPRESS Trial: Algenpantucel-L vaccine with chemoradiation therapy for patients with resectable PDA

Tumor-specific cancer cell lines modified to express the carbohydrate alpha-gal

PILLAR trial open for patients with locally advanced non resectable disease NCT01836432
Combining vaccines with checkpoint antibody for patients with pancreatic cancer

Dual component gene therapy vaccine
• GVAX pancreas – irradiated, whole cell tumor vaccine, secretes GM-CSF
• LADD Listeria – live, attenuated Listeria monocytogenes expressing mesothelin
• Survival benefit in patients given both components rather than GVAX alone, now a randomized study nationwide, NCT02004262
• Next step is to add anti-PD-1 antibody (trial at Johns Hopkins to open soon, NCT02243371)

GVAX plus ipilimumab
• Patients who receive FOLFIRINOX then go on to receive GVAX pancreas plus anti-CTLA-4 antibody (trial at Johns Hopkins, NCT01896869)

The road to personalized cancer vaccines

Vonderheide and Nathanson, Nature Medicine, 2013
Engineered T cell therapy for pancreatic cancer

1. Remove the immune cells from blood
2. Engineer killer lymphocytes in a clinical laboratory
   - Anti-mesothelin
   - NCT01897415
3. Prepare cells for re-infusion
4. Give patient engineered T cells

Porter et al, NEJM, 2011
Grupp et al, NEJM, 2013
Maude et al, NEJM, 2014
Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory

Before treatment

After treatment

Beatty et al, Science, 2011
CD40 antibody immune therapy for pancreatic cancer

Beatty et al, Science, 2011

CD40 antibody for patients undergoing surgery

To open soon at Penn: Phase I study of preoperative CD40 antibody +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma

CD40 antibody +/- Gem/nab-paclitaxel

Dx Resect Gem/nP + CD40 antibody x 4 cycles

Day 1 15 Safety observe Outcome

Tissue and blood biomarkers
Recalcitril with chemotherapy for patients with resectable pancreatic cancer

- Expression profiling of tumor stellate cells revealed Vitamin D receptor as a potential regulator of function. *Sherman et al., Cell, 2014*
- Vitamin D agonists alter tumor stroma and facilitate tumor death in combination with chemotherapy in laboratory studies
- Phase I study of paricalcitol and chemotherapy delivered prior to, and again after, surgical resection of primary tumor
  - At Penn, NCT02030860

Mutant Kras oncogene

- More than 95% of all patients with pancreatic ductal adenocarcinoma have mutations in Kras in the tumor
- There are cooperating mutations but no other common ‘driver’ mutations
- Does mutant Kras cause such immune suppression?

*Pasca di Magliano and Logsdon, Gastroenterology, 2013*
*Bakin et al., Nature, 2012*
The Ras Initiative

http://www.cancer.gov/researchandfunding/priorities/ras

Pancreatic cancer is a clinical EMERGENCY
Research in clinical trials are critical

Still, only 4% of patients with pancreatic cancer ever go on a clinical trial

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 our Patient and Liaison Services (PALS) program at (877) 272-6226 or e-mail pals@pancan.org.

www.pancan.org or wagehope.org