Cancer Immunotherapy and Radiotherapy Immune Modulation

Magical Effects of the healing beam?

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  - Incyte
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  - BMS
Immunotherapy: A Revolution in Cancer Therapy
What Is the Immune System

- Main function: recognition of “self” from “non-self” and eliminate “non-self”
How Immune System recognizes non self

**Innate Immunity**
- Pathogen Associated Molecular Patterns (proteins, carbohydrates, lipids, nucleic acids)
- PRRs
- Mφ
- Pathogen phagocytosis and elimination

**Adaptive Immunity**
- Naïve T-cell
- Ag presentation
- Co-stimulatory molecules
- Cytokines/Chemokines
- CTL
- Th1
- Th2
- Th17
- Treg
- B cell
- Antibody production
Historical Perspective

1909: Paul Ehrlich proposes concept of immunosurveillance


1950’s-1980’s: Lewis Thomas proposes that the transplant rejection is actually a manifestation of immunosurveillance.

Immunoediting

- Dunn et al. Immunity 2004 (21) 137-148
Timeline of the Development of Immunotherapy

- **1891**: First cancer "vaccine" demonstrated (Coley bacterial toxin)
- **1909**: Cancer occurs spontaneously; immune system recognizes and protects (Elrich)
- **1960s**: Adjuvants (e.g., BCG) shown to eradicate some tumors
- **1960**: BCG approved for bladder cancer
- **1985**: Adoptive immunotherapy for patients with cancer
- **1986**: IFNα approved as cancer immunotherapy
- **1990**: Sipuleucel-T approved as first autologous cellular immunotherapy
- **1992**: IL-2 approved as cancer immunotherapy
- **1990**: Ipilimumab approved for metastatic melanoma

**Notes:**

BCG = Bacille Calmette-Guérin
IFN = interferon
IL = interleukin
TIL = tumor-infiltrating lymphocyte

Nature Milestones Cancer 2006; S7-S23.
Complex interplay between the host immune cells and the tumor and its microenvironment.
Antigen-presenting cell

- PDL1 or PDL2
- PDL1 or PDL2
- CD80 or CD86
- CD80 or CD86
- B7RP1
- B7-H3
- B7-H4
- HVEM
- Peptide (MHC class I or II)
- CD137L
- OX40L
- CD70
- CD40
- GAL9
- Adenosine

T cell

- PD1
- CD28
- CTLA4
- ICOS
- BTLA
- KIR
- TCR
- LAG3
- CD137
- OX40
- CD27
- CD40L
- TIM3
- A2aR

Cytokines (TGFβ, IL-1, IL-6, IL-10, IL-12, IL-18)

Signal 1
WE CAN CURE CANCERS PREVIOUSLY THOUGHT TO BE INCURABLE

ONLY A MINORITY OF PATIENTS RESPOND TO TREATMENT

Bellmunt et al– NEJM- 2017
Pitt et al. Immunity 2016
• Pulluri et al. Pharmacological Research 2017
Exclusion of Tumor Infiltrating T-cells is a mechanism of resistance to checkpoint blockade

Spranger, Bao, Gajewski - Nature 2015
Radiation: beyond cytotoxicity
Not convinced?

... Two Case Reports of accidental irradiation, circa 1962

- Dayton, Ohio
- Forest Hills, New York
Immunomodulatory Effects of Radiotherapy

Tumor debulking and releasing tumor antigens
Not systemically immunosuppressive
Up regulation of immunogenic cell surface markers
- ICAM-1
- MHC-1
- Fas

Secretion of danger signals & cytokines
- IFN-γ
- TNFα
- IL-1β

Induction of Immunogenic cell death
- Calreticulin
- HMGB-1

Increased homing of immune cells to tumors
- Normalization of tumor vasculature
- Secretion of chemo-attractants (cxcl16)
- Endothelial expression of VCAM-1
- Improved T-cell homing to tumors

Improved antigen presentation by APC’s
- Irradiated tumors prime dendritic cells
- Improved antigen presentation via TLR-4

Depletion of immunosuppressive cells

Shifting TAM polarization to M1

Obeid et al. CDD. 2007; 18: 1848
Apetoh et al. Nature Medicine. 2007; 13(9): 1050
Ganss et al. Ca Research. 2002; 62: 1462
Strome et al. Ca Research. 2002; 62: 1884
Apetoh et al. Nature Medicine. 2007; 13(9): 1050
Upregulation of Immunogenic Cell Surface Markers

Graphical data showing the upregulation of Fas and ICAM-1 in MC38 and MC38-CEA+ cells. The graphs compare the expression levels before and after radiation treatment.

Other graphs illustrate the lymphocyte-mediated killing of MC38 cells in the presence of anti-Fas-L and anti-ICAM-1 antibodies. Tumor growth curves are also shown for different treatments, including no treatment, irradiation, and irradiation with different T-cell subsets.
Normalization of Tumor Vasculature

Ganss et al. Ca Research. 2002; 62: 1462
Increased T-cell Infiltration


Improved Survival

Ganss et al. *Ca Research.* 2002; 62: 1462

Klug et al. *Cancer Cell.* 2013;24:589-602
Pancreatic Tumor Progression Treated with NK cells and Local Radiation

A) Tumor cell injection into flank
B) Inject activated NK cells into tumor

~2-3 weeks for tumor to develop

Local irradiation, 8cGy

5 days
A. CD4+ Subsets
- Effector Memory CD4+ T cells (CD45RA- CD62L+)
- Central Memory CD4+ T cells (CD45RA+ CD62L+)

B. Percent Memory CD4+ of Total Lymphocytes
- Parenchymal
- Bone
- Brain

C. Percent ICOS+ Memory CD4+ of Total Lymphocytes

D. Percent CD25+ Memory CD4+ of Total Lymphocytes

E. Comparing Pre-RT (solid) and Post-RT (hashed)
- p=0.08

UC DAVIDS
# Preclinical evidence for synergy between radiation and PD-1 pathway inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Radiation Dose</th>
<th>Timing</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng et al. JCI 2014</td>
<td>TUBO (breast)</td>
<td>12 Gy x 1</td>
<td>4 doses starting with radiation</td>
<td>- Tumor growth</td>
</tr>
<tr>
<td></td>
<td>MC38 (colon)</td>
<td>20 Gy x 1</td>
<td></td>
<td>- Rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Contralateral tumor growth</td>
</tr>
<tr>
<td>Dovedi et al. Can Res 2014</td>
<td>4T1 (breast)</td>
<td>2 Gy x 5 or 4</td>
<td>3qw for 3 weeks starting day 1 or day 5</td>
<td>- Tumor growth</td>
</tr>
<tr>
<td></td>
<td>CT26 (colon)</td>
<td>Gy x 5</td>
<td></td>
<td>- Survival</td>
</tr>
<tr>
<td></td>
<td>4434 (melanoma)</td>
<td></td>
<td></td>
<td>- Rechallenge</td>
</tr>
<tr>
<td>Sherabi et al. CIR 2014</td>
<td>B16 (melanoma)</td>
<td>12 Gy x 1</td>
<td>3 injections every 3 days starting 1 day before RT</td>
<td>- Tumor growth</td>
</tr>
<tr>
<td></td>
<td>4T1 (breast)</td>
<td></td>
<td></td>
<td>- Rechallenge</td>
</tr>
<tr>
<td>Tywman-Saint Victor et al.</td>
<td>B16 (melanoma)</td>
<td>20 Gy x 1</td>
<td>3 injections every 3 days starting 3 days before or 1</td>
<td>- Tumor growth</td>
</tr>
<tr>
<td>Nature 2015</td>
<td>TSA (breast)</td>
<td>8 Gy x 3</td>
<td>day after RT</td>
<td>- Survival</td>
</tr>
<tr>
<td></td>
<td>PDA (pancreatic)</td>
<td>20 Gy x 1</td>
<td></td>
<td>- Contralateral tumor growth</td>
</tr>
<tr>
<td>Zeng et al. IJROBP 2013</td>
<td>GL261 (glioma)</td>
<td>10 Gy x 1</td>
<td>3 injections 2 days apart starting with RT</td>
<td>- Tumor growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Rechallenge</td>
</tr>
</tbody>
</table>
### Selected trials testing PD-1 pathway inhibitors and radiation therapy

<table>
<thead>
<tr>
<th>Histology</th>
<th>Stage</th>
<th>Agent</th>
<th>Type of RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>SBRT or Conformal</td>
</tr>
<tr>
<td>SCLC</td>
<td>Limited or extensive</td>
<td>Pembrolizumab+ Carboplatin+Etoposide</td>
<td>Conformal</td>
</tr>
<tr>
<td>H&amp;N, RCC, NSCLC Skin, Melanoma</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>Conformal, multiple regimens</td>
</tr>
<tr>
<td>Glioma</td>
<td>Recurrent</td>
<td>Pembrolizumab+ Bevacizumab</td>
<td>SRT</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>Unspecified</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>SBRT</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>Localized</td>
<td>Pembrolizumab</td>
<td>Fractionated</td>
</tr>
<tr>
<td>Pancreatic cancer, Melanoma, NSCLC, breast</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Melanoma, NSCLC</td>
<td>Metastatic</td>
<td>Pembrolizumab</td>
<td>SBRT</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Metastatic</td>
<td>Pembrolizumab+ Capecitabine</td>
<td>Fractionated</td>
</tr>
<tr>
<td>Breast</td>
<td>Oligometastatic</td>
<td>Pembrolizumab</td>
<td>SBRT</td>
</tr>
<tr>
<td>H&amp;N</td>
<td>Locally recurrent</td>
<td>Pembrolizumab</td>
<td>Fractionated</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Unresectable</td>
<td>Durvalumab</td>
<td>SBRT</td>
</tr>
<tr>
<td>GBM</td>
<td>Upfront</td>
<td>Durvalumab</td>
<td>Fractionated</td>
</tr>
<tr>
<td>NSCLC</td>
<td>IIIA/IIIB</td>
<td>Nivolumab</td>
<td>Fractionated</td>
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<tr>
<td>Multiple histologies</td>
<td>Metastatic</td>
<td>REGN2810</td>
<td>SBRT</td>
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<tr>
<td>NSCLC</td>
<td>Metastatic</td>
<td>MPDL3280</td>
<td>SBRT</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Metastatic</td>
<td>MPDL3280</td>
<td>SBRT</td>
</tr>
<tr>
<td>Colon</td>
<td>Metastatic</td>
<td>AMP224</td>
<td>Unspecified</td>
</tr>
</tbody>
</table>
Rebound Immune Suppression

- Radiotherapy
- Cell Stress
- Acute Inflammation
- Chronic Inflammation
- Immune Suppression

Reactivity | Immunological Homeostasis | Tolerance
RT alone rarely induces a ‘systemic’ anti-tumor response but needs to be combined with immunotherapy to get a true *abscopal* effect.
Radiotherapy modulation of TAMs

In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study

IDO expression is up-regulated by inflammatory therapies.
IDO blockade improves anti-tumor effects of RT + CpG
Canine trial: abscopal response
**General Enrollment Criteria**

- Advanced refractory solid tumors or lymphoma
- Age ≥18
- 14 day treatment washout period
- At least one candidate treatment lesion (subcutaneous, nodal, or visceral)
  - Accessible for RT
  - Accessible and safe for repeat intralesional injections
- At least one candidate target lesion, outside of the RT field evaluable for response per irRECIST
- Adequate hematologic and end organ function
- No active autoimmune disease
- Patients with previous checkpoint blockade therapy are eligible

**Concurrent RT (Days 1-5)**
- Cohort 1 (solid tumors): (8 Gy x 3) or (4 Gy x 5)
- Cohort 2 (lymphoma): (8 Gy x 3) or (4 Gy x 5) or (2 Gy x 2)
- Intralesional SD-101 (Day 1, 8, 15, 22, 29)
  - 4 mg injection into RT treatment lesion
  - Epacadostat
  - 100-300 mg PO bid
Selected Cancer Immunotherapy Targets/Strategies

- **Inhibitory Signals**
  - CTLA-4, PD-1/PD-L1, LAG-3, TIM-3, VISTA, BTLA

- **Stimulatory Signals**
  - ICOS, CD40, OX40, 41BB

- **Cytokines**
  - IL-2, IL-12, IL-15, TGF-beta blockade

- **CARS**

- **Adoptive Cell Transfer**

- **Vaccines**
  - PANVAC, Provenge

- **Oncolytic Virus**

- **TLR agonists**

- **Inhibitory Enzymes**
  - IDO, Arginase
RT + HD systemic IL-2

ORR: 66%
Historical response rate: 10-15%

preclinical data: RT + intrallesional IL-2
Recurrent Melanoma
2 Years Later
Key Points

• Radiotherapy has diverse immune modulatory effects
• Clinically significant anti-tumor responses from radiotherapy alone are rare
• There is a Potent synergy potential of RT + IT
• It is a complex system – best combinatorial strategies are likely to also be complex (not the simple addition of adding a short course of IT)
• Best strategy may depend on stage, histology, immunotherapy, patient factors, and desired effect
Questions

• Which / how many lesions to treat for an abscopal effect?
• Sequencing / timing?
• Dose / fractionation? (eg. Conventional vs SBRT?)
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