Optimizing Immunotherapy with Radiation

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Overview

• Background: Rationale for Radiotherapy/Immunotherapy Combinatorial Strategies
  – Mechanisms of Synergy

• Radiation: Do target organ, sequencing with drug, dose, and fractionation matter?

• Current and Emerging Clinical Evidence

• Next Directions
Classes of Immunotherapy

**Vaccinations**
Similar to infection vaccines, retrained immune cells to recognize tumor associated antigens.

**Strong Immune Stimulants**
General activation of the immune system in a non-specific manner.

**Chimeric Antigen Receptor (CAR) NK & T Cell Therapy**
Empowering T cells and NK cells with engineered receptors to recognize cancer, then infuse back.

**Inhibitory Checkpoint Blockade**
Releases the brakes of the immune system and/or steps on the gas.
Immunotherapy Combinatorial Strategies

**Approaches**
- Dual Immunotherapy
  - Dual checkpoint blockade
  - Checkpoint blockade/stimulatory agonist
  - Other
- Immunotherapy/Chemotherapy
- Immunotherapy/Radiotherapy

**Open Questions for IO/RT strategies**
- Sequencing/Timing
- Optimization
  - Radiation dose, fractionation, and site
- Synergistic toxicities
Rationale for Radiation/Immunotherapy Combinatorial Strategies

- Tumor debulking/release of tumor antigens
- Upregulation of immunogenic cell surface markers
- Secretion of cytokines/danger signals
- Induction of immunogenic cell death
- Increased homing of immune cells to tumor
- Improved antigen presentation by APCs
- Depletion of immunosuppressive cells
- Shifting TAM polarization to M1
- Up-regulation of cell-surface PD-L1
Mechanisms of Radiation-Induced Immune Activation

Daly ME, Monjazeb AM, Kelly K. Journal of Thoracic Oncology 2015
Immunotherapy/RT Combinatorial Strategies: Current Status

• Preclinical Data
  – Effects of RT on the immune system dependent on irradiated site
  – Data for dose and fractionation
  – Data for timing of IO and RT

• Retrospective Clinical Data
  – Case reports/series
  – Secondary analyses of prospective trials

• Prospective Clinical Trials
  – Metastatic Disease
  – Localized Disease
Effects of RT on the Immune System

• RT traditionally thought of as immunosuppressive, related to irradiation of marrow and circulating blood

• However, effects of focal, high-dose radiation appear to be more complex

  – Pilot study evaluating effects of SBRT on peripheral blood immunophenotype and cytokine/chemokine profiles from 40 patients treated with SBRT to lung, liver, bone, or brain identified changes in NK and T cell subsite that appear to related to irradiated site
  – Obtained peripheral blood samples pre- and 1 week post-SBRT

McGee H et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. IJROBP Aug 2018
Effects of RT on the Immune System

McGee H et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. IJROBP Aug 2018
# Does Dose/Fractionation Matter?

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Dose/Treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Lugade *et al*, 2005| Murine; heterotopic melanoma       | • 15 Gy x 1  
• 3 Gy x 5 | • Improved tumor control with 15 Gy  
• Increased immunogenic APCs with 15 Gy x 1  
• Increased infiltration of immune cells at day 14 with 15 Gy x 1 |
| Schaue *et al*, 2012| Murine; heterotopic melanoma       | • 15 Gy in 1, 2, 3, or 5 fx  
• Single fx of 5, 7.5, 10, or 15 Gy | • 15 Gy in 2 fractions provided the best tumor control and tumor immunity while maintaining low Treg numbers. |
| Dovedi *et al*, 2013| Murine lymphoma model              | TLR7 agonist +  
• 10 Gy x 1  
• 2 Gy x 5 | • Fractionation enhanced tumor response mouse and survival as compared to single fraction |
| Dewan *et al*, 2009 | Murine breast model, 2 sites       | Anti-CTLA4 +  
• 20 Gy x 1  
• 8 Gy x 3  
• 6 Gy x 5 | • Anti-CTLA4 + 8 Gy x 3 or 6 Gy x 5 generated abscopal effect in unirradiated tumor.  
• No effect for 20 Gy x 1 |
| Verbrugge *et al* 2012 | Murine triple negative breast model | • Anti CD137/anti-PD-1  
• 4 Gy x 4  
• 4 Gy x 5  
• 12 Gy x 1 | • 12 Gy x 1 100% response  
• 4 Gy x 4 40% response  
• 4 Gy x 5 80% response |
Does Timing Matter?

- Tumor bearing mice were treated with 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody.
- Anti-CTLA-4 was most effective when given prior to RT.
- OX40 agonist was most effective when delivered following RT.
- Suggests optimal timing of immunotherapy and RT depends on mechanism of immunotherapy action.

Young KH et al. Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy. PLOS One. 2016 Jun 9;11(6):e0157164
Does Timing Matter?

- Retrospective Review of patients treated with ipilimumab and non-brain directed RT for melanoma
- Median OS was 9 months for RT given during induction and 39 months for RT during maintenance
- Difference may be due to selection bias, but provocative

Clinical Data: Current Status

• Case reports/series
  – NYU, many other

• Secondary analyses of prospective trials
  – KEYNOTE 001

• Prospective trials
  – Few published, many ongoing
KEYNOTE-001: Pembrolizumab for the Treatment of NSCLC

Tumor PD-L1 expression established as a biomarker for increased likelihood of response

Secondary Analysis of KEYNOTE-001: Effect of Prior Radiotherapy on PFS and OS

IO/RT Strategies: Prospective Clinical Trials

Hundreds of registered trials across most solid tumors/heme malignancies

- NSCLC
- Breast Cancer
- Sarcoma
- Melanoma
- Urothelial Cancers
- Pancreatic Cancer
- Prostate Cancer
- Merkel Cell
- Mesothelioma
- Head and Neck Cancer
- Adenoid Cystic Carcinoma
- Glioblastoma
- Renal Cell
- Colorectal Cancer
- Follicular Lymphoma
- Cervical Cancer
- Ovarian Cancer
- Anaplastic thyroid
- Esophageal Cancer
- Primary CNS Lymphoma
- Solitary plasmacytoma
- Uterine Cancer
### Published Prospective Clinical Trials using RT+IO agent in metastatic setting

<table>
<thead>
<tr>
<th>Institution</th>
<th>Tumor Type</th>
<th>IO agent</th>
<th>RT</th>
<th>N</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYU</td>
<td>Solid tumor</td>
<td>GM-CSF</td>
<td>35 Gy/10 fractions</td>
<td>41</td>
<td>Abscopal response rate</td>
</tr>
<tr>
<td>Yale</td>
<td>Melanoma (brain mets)</td>
<td>ipilimumab</td>
<td>WBRT 30/10 or single fx SRS</td>
<td>16</td>
<td>MTD and safety</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>Solid tumor</td>
<td>ipilimumab</td>
<td>SBRT lung or liver 50/4 or 60/10</td>
<td>35</td>
<td>Safety</td>
</tr>
<tr>
<td>Stanford</td>
<td>melanoma</td>
<td>ipilimumab</td>
<td>Palliative RT, variety of schemas</td>
<td>22</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Earle A. Chiles Research Inst.</td>
<td>melanoma</td>
<td>IL-2</td>
<td>SBRT 20 Gy x 1, 2, or 3</td>
<td>12</td>
<td>MTD</td>
</tr>
<tr>
<td>Netherlands Cancer Institute</td>
<td>NSCLC</td>
<td>NHS-IL2</td>
<td>Palliative RT 20/5 to lung nodule</td>
<td>13</td>
<td>MTD</td>
</tr>
<tr>
<td>Stanford</td>
<td>Low grade lymphoma</td>
<td>CpG</td>
<td>2 Gy x 2</td>
<td>15</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>U Penn</td>
<td>melanoma</td>
<td>ipilimumab</td>
<td>12-24 Gy in 2-3 fx</td>
<td>22</td>
<td>Toxicity and response</td>
</tr>
</tbody>
</table>
Phase I IL-2+SBRT in Melanoma and RCC

- 11 patients
- SBRT 20 Gy x 1-3 followed by high-dose IL-2
- 8/12 patients (66.6%) CR or PR

Seung SK et al. Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—Tumor and Immunological Responses. Sci Transl Med 2012;4:137ra74
Stanford Pilot Study: Ipilimumab+ Palliative RT in Metastatic Melanoma

- 22 patients enrolled
- A variety of RT schedules were used, including SBRT in some patients
- 50% had clinical benefit, including CR, PR, and SD

Hiniker SM et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. IJROBP Nov 2016.
NYU: GM-CSF+RT Pilot Trial in Metastatic Solid Tumors

- 41 patients with stable or progressing solid tumors enrolled
- RT 35 Gy/10 fx delivered with GM-CSF sub-q daily for 2 weeks starting RT week 2
- Course repeated targeting a second site
- 11/41 patients had abscopal responses (out-of-field) (4 NSCLC, 5 breast, 2 thymic)

Intratumoral CpG with low dose RT for Low Grade Lymphoma

- 15 patients with refractory low grade lymphoma enrolled
- CpG given with low dose RT 2 Gy x2
- 1 CR, 3 PR, and 2 long-duration stable disease

Moving Immunotherapy/RT Strategies to Earlier Stage Disease

Non-Small Cell Lung Cancer (NSCLC) as an example
  • Locally Advanced disease
  • Early Stage Disease
Moving Checkpoint Inhibitors to Earlier Stages: PACIFIC Trial: Stage III NSCLC

Randomized Phase III Multicenter Trial

Stage III NSCLC patient, Treated with definitive CRT

2:1 randomization

1. Placebo

2. MEDI4736 10 mg/kg IV Q2 wk, up to 12 months

Primary Objectives
- OS (RECIST 1.1)
- PFS (RECIST 1.1)

Secondary Objectives
- proportion of patients alive at 24 months
- ORR
- safety and tolerability
- Pharmacokinetics
- Immunogenicity of MEDI4736
- symptoms and HR-QOL

Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer
PACIFIC results: PFS in the Intention-to-Treat Population.
Eligibility: T1-2N0 NSCLC, medically inoperable or refused surgery
One of more high risk feature:
Tumor diameter ≥ 2 cm
Tumor SUV max ≥ 6.2
Grade 3 histology

Primary Outcome: MTD of MPDL3280A that can be given with SAR in patients with inoperable stage I NSCLC.

Secondary Outcomes: Safety profile of this regimen using CTCAE v4
Preliminary efficacy data of the combination as determine by ORR and DFS using RECIST 1.1

Exploratory Objectives
To analyze serial blood for change in cytokine signatures, FACS and immunophenotyping of peripheral blood mononuclear cells (PBMCs) and tumor infiltrating immune cells.
To evaluate pre and post treatment tumor tissue (if available) for PD-L1 and other immune proteins in the tumor and tumor microenvironment and for molecular profiling in a subset of patient samples.
Summary/Next Directions

- Immuno-oncology strategies have altered the landscape of cancer therapies
- Radiation is an intriguing partner therapy
- Additional preclinical and clinical studies are needed to guide details of RT
  - Dose/fractionation
  - Site treated
  - Timing
- The vast array of actively accruing human clinical trials in this space should provide significant insights into this strategy once completed
Acknowledgements

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