Radiation and Immune Modulation: Implications for Clinical Practice

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Disclosures

- Medical Director, SCCA Proton therapy at University of Washington
- Apollo Oncology Advisory Group
Introduction

- Primary cause of death for patients with advanced solid tumors is metastatic progression of disease

- In recent years, subsets of patients with metastatic disease have been identified for whom long-term survival may be dictated by local control
  - “Oligometastatic” patients for whom locally ablative therapy to all sites of disease can achieve ‘cure’
  - “Oligoprogresive” patients for whom locally ablative therapy may prolong PFS
    - Particularly valuable in the era of targeted therapy (Gan et al IJROBP 2014)

- What about the 80-90% of stage IV disease in whom systemic progression determines outcome?
  - Delivery of selective therapy to sterilize tumor without damaging normal tissue remains a challenge
Introduction: Therapeutic Index

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PROBABILITY

<table>
<thead>
<tr>
<th>TREATMENT INTENSITY</th>
</tr>
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<tbody>
<tr>
<td>Normal tissue exposure</td>
</tr>
<tr>
<td>Treatment Intensification</td>
</tr>
</tbody>
</table>

The promise of cancer immunotherapy

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Tumor control

Toxicity
Clinical design

676 HLA-A2+ pts with met melanoma
Progression despite one prior Rx
Ipi vs. gp100 vaccine vs. both q3wk x 4

Results

Ipi arms extended median survival by 4mo
Improved 1 yr survival by 72%
(from 25% to 43%)
ORR 11% ipi vs. 1.5% with vaccine alone
Phase III Trial of CTLA-4 Blockade with Ipilimumab

- Overall response rate of 11% for patients receiving ipilimumab
- Why did 80+% of patients fail to respond?
Clinical approach to immunomodulation: Cutting off the brakes

CTLA-4 Feedback Pathway

Proliferation

Inhibition
Clinical approach to immunomodulation: Cutting off the brakes

CTLA-4 (PD-1) Blockade is only effective if antigen presentation has occurred

Proliferation

No inhibition
What is the potential role for radiation in this paradigm?
- 52 yom with ‘malignant lymphoma NOS’
  - Bilateral pleural effusions
  - Pulmonary parenchymal disease
  - Hepatosplenomegaly on exam
  - Palpable cervical, axillary, inguinal adenopathy

- 1-month post-RT
  - No palpable adenopathy
  - Resolution of hepatosplenomegaly

- 3 months post-RT
  - Normalization of CXR
The tumor conveyor belt and the abscopal effect

- Initial observation of the abscopral effect was restricted to “liquid” tumors
- What is the relevance of the abscopal effect for solid tumors?
Metastatic lung adenocarcinoma

The ‘abscopal’ effect

Siva et al Cancer Letters 2013
Radiation therapy

Adapted Hodge et al Oncology 2008
Why do we rarely see immune cooperation with RT? Are we looking in the right place?
Early Stage Disease: Stereotactic Body Radiation Therapy

- Control rate with SBRT 95-98%
- Can we really attribute this to dose intensification?
Immune Cooperation with RT: Is there relevance for the primary tumor response to radiation?

Lee et al. Blood 2009
SBRT: Potential immune cooperation?

- Why is SBRT apparently superior to a wedge?
- Why is there superior regional nodal control when neither approach treats the nodes?
- Is this a clinical example of immune cooperation with RT?
Why do we rarely observe the abscopal effect?
Sufficient dose to achieve immunogenic cell death

Antigen Processing And Presentation

Checkpoint Inhibition

Immunogenic tumor
Preclinical data to support hypofractionated radiation

- Syngeneic xenograft model has provided critical data on the abscopal effect
- Suggests cooperation between hypofractionated radiotherapy and immune checkpoint inhibition
- Suggest that dose and fraction size impact on the efficacy and magnitude of cooperation


©2009 by American Association for Cancer Research
Abscopal effect in melanoma patient after treatment with CP-870,893 and tremelimumab

Baseline
1-11-11

4 weeks
2-8-11

5 months
6-24-11

Treme: 1-13-11
CD40: 1-14-11

Left c.w. XRT to tumor (outlined in red): 1-31-11 to 2-14-11
300cGy x 10
Stratified phase I/II dose escalation trial of stereotactic body radiotherapy followed by ipilimumab in metastatic melanoma

**Hypofractionated RT to single ‘index’ lesion**
(over 3-7 days)

- Stratum 1: lung or bone
  - 8 Gy x 3
  - (DL-1 of 8Gy x 2)
- Stratum 2: liver or s.c.
  - 6 Gy x 3
  - (DL-1 of 6Gy x 2)

**ipilimumab i.v. q3weeks x 4**
1st ipi 5 days after RT

- Follow up Restaging
- Biosamples and analysis

Clinicaltrials.gov NCT01970527
PI, Rengan/Maity/Hahn
- Stage IV melanoma (any number of priors)
- Index lesion ≥1 cm
- ECOG PS 1-0
Tumor response to SBRT/ipilimumab

Baseline

4d s/p SBRT

2mo s/p ipi #4

SBRT to index lesion

RECIST: -68% (exclude index)

Twyman-Saint Victor Nature 2015 Apr 16;520(7547):373-7
Clinical Results

- 18% of patients had a partial response as best response
- Some major regressions were seen (PT-402)
- None of the irradiated tumors had progressive metabolic disease as evaluated by PET
- Resistance was common, however
Tumor Predictors

- Tumor PD-L1 expression was associated with likelihood of T-cell exhaustion (inhibition) in clinical trial patients.
- Mouse model revealed tumor PD-L1 expression was negatively associated with PFS and OS.
- Follow-up clinical trial of RT + anti-CTLA4 + anti-PD1 is now ongoing.

<table>
<thead>
<tr>
<th>RECIST</th>
<th>PD-L1(lo)</th>
<th>PD-L1(hi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Twyman-St. Victor Nature 2015
Open questions in radiation and immune modulation
Immune Cooperation with RT:

- How do we safely combine radiation immune checkpoint inhibition?
  - What is the optimal dose/fractionation and volume?
  - What is the optimal index lesion location?
  - What have we learned from clinical trials to date?

- How do we know if we have generated a T-cell response against the tumor?
  - What are the immune correlates of response?
  - What tumor genomic characteristics are favorable for immunogenicity?

- What are the normal tissue considerations when combining radiation with immunotherapy?

- What are the ongoing clinical trials in radiation and immune modulation?
Thank You
Clinical Trials of Radiation and Immunotherapy

Jonathan Schoenfeld
Brigham and Women’s / Dana-Farber Cancer Center
Boston, MA
Disclosure

Employer: Brigham and Women’s Physicians Organization

Potential Conflicts of Interest: funded clinical trials (BMS, Merck), SAB (BMS, Debiopharm)

I WILL discuss investigational uses of immunotherapy.
Learning Objectives

• To discuss data combining radiation (RT) and immuno-oncology agents (IO)

• To discuss planned studies and considerations in RT+IO clinical trial design such as response and correlative studies
There is a strong preclinical rationale for testing radiation and immunotherapy in clinical trials

- Immunotherapy enhances the LOCAL effects of radiation
- Radiotherapy potentiates the SYSTEMIC effects of immunotherapy (abscopal, out-of-field responses, vaccine-like effects)

Synergy observed across IO agents and classes

- TGF beta-inhibitors
- CTLA-4 inhibitors
- PD-1/PD-L1 inhibitors
- STING/TLR activators
- IL2, Flt3 ligand, GM-CSF
- OX40, 4-1BB agonist

Adapted from Smyth et al. Nat Reviews Clin Oncol 2016
Clinical experiences also suggest synergy for RT with checkpoint inhibitors

Abscopal response with immune potentiation in a melanoma patient treated with ipilimumab + RT

Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy

Tolerability of Combined Treatment

Bang et al. IJROBP 2017

- Retrospective analysis of 133 consecutive patients with metastatic melanoma, RCC, NSCLC who received palliative radiation and CTLA-4 and/or PD-1 blockade (105 patients received PD-1 inhibitors)
- 39 patients received concurrent treatment, 56 within 14 days

<table>
<thead>
<tr>
<th>Baseline non-dermatologic Ir-AEs in study (n=113)</th>
<th>Grade 1-2</th>
<th>Grade 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>IrAE that developed with an associated site of radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with radiation to the lung with pneumonitis (n=34)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with radiation to the bowel with colitis (n=26)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with radiation to the brain with hypophysis (n=71)</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Patients with radiation to the neck with endocrinopathies (n=74)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with radiation to the abdomen with transaminitis (n=26)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IrAE that developed without an associated site of radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without radiation to the lung with pneumonitis (n=79)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Patients without radiation to the bowel with colitis (n=87)</td>
<td>4 (5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Patients without radiation to the brain with hypophysis (n=42)</td>
<td>0 (0%)</td>
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<td>5 (6%)</td>
<td>2 (2%)</td>
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Completed Trials: RT + Ipitimumab
Kwon et al. Lancet Oncology 2014

• **Eligibility:** Castrate-resistant prostate cancer patients (previously failed docetaxel) with at least 1 bone metastasis

• **Treatment:** Palliative radiation (8 Gy x 1) +/- ipilimumab 10 mg / kg

• **Primary endpoint:** Overall survival
Completed Trials: RT + Ipilimumab
Kwon et al. Lancet Oncology 2014

• Outcome (n=799): negative trial, but trend towards benefit in overall survival
  – median survival 11.2 vs. 10 months, p=0.053
  – several early deaths and then an apparent benefit

• Potentially critical impact of patient selection, ipilimumab dose, RT dose/fractionation/site
# Prospective Non-randomized Studies

## Radiation + Ipilimumab (ipi)

<table>
<thead>
<tr>
<th>Study</th>
<th>RT dose / site</th>
<th>Timing</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiniker et al. IJROBP 2016 (melanoma)</td>
<td>Variable (1-15 fx) - BED$_{10}$ 28-112.5 Liver, lung, neck, etc. (3D, IMRT, SBRT)</td>
<td>RT given 5 days after starting ipi</td>
<td>27% RR (14% CR), 50% CBR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang et al. CCR 2016 (NSCLC, CRC, sarcoma, RCC) n=35</td>
<td>50-60 Gy in 4 or 10 fractions (lung and liver)</td>
<td>RT day after 1$^{st}$ ipi or week after 2$^{nd}$ dose</td>
<td>10% PR, 23% CBR</td>
</tr>
<tr>
<td>Tywan-St.Victor et al. Nature 2015 (melanoma) n=22</td>
<td>8 Gyx 2-3 (lung/bone) 6 Gyx2-3 (liver/subQ)</td>
<td>RT then ipi started 3-5 days later</td>
<td>18% PR, 18% SD</td>
</tr>
</tbody>
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Development of numerous RT+IO trials

- Johnson and Jagsi IJROBP 2016:
  81 ongoing trials testing radiation-immunotherapy combinations

Adapted from Johnson and Jagsi IJROBP 2016
Development of numerous RT+IO trials

• Johnson and Jagsi IJROBP 2016: 81 ongoing trials testing radiation-immunotherapy combinations

Adapted from Johnson and Jagsi IJROBP 2016
Endpoints in Immunotherapy Trials: Response Underestimates Benefit

Hodi et al. NEJM 2010
Endpoints in Immunotherapy Trials: Atypical Patterns of Response on PD-1 blockade

Hodi et al. JCO 2016
Endpoints in Immunotherapy Trials: Immune Response Criteria (irRC)

<table>
<thead>
<tr>
<th>Category</th>
<th>RECIST v1.1</th>
<th>irRC</th>
</tr>
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<tbody>
<tr>
<td>Measurement of tumor burden</td>
<td>Unidimensional</td>
<td>Bidimensional</td>
</tr>
<tr>
<td>Target lesions</td>
<td>Maximum, 5*</td>
<td>Maximum, 15 index lesions</td>
</tr>
<tr>
<td>New lesion</td>
<td>Results in progressive disease at first appearance</td>
<td>Up to 10 new visceral lesions and 5 cutaneous lesions may be added to the sum of the products of the two largest perpendicular diameters of all index lesions at any time point</td>
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<td>Complete response</td>
<td>Disappearance of all target and nontarget lesions</td>
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<td>Nodes must regress to &lt; 10 mm short axis</td>
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<tr>
<td></td>
<td>Confirmation required</td>
<td>Confirmation required</td>
</tr>
<tr>
<td>Partial response</td>
<td>( \geq 30% ) decrease in tumor burden compared with baseline</td>
<td>( \geq 50% ) decrease in tumor burden compared with baseline†</td>
</tr>
<tr>
<td></td>
<td>Confirmation required</td>
<td>Confirmation required</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>( \geq 20% + 5)-mm absolute increase in tumor burden compared with nadir</td>
<td>( \geq 25% ) increase in tumor burden compared with baseline, nadir, or reset baseline†</td>
</tr>
<tr>
<td></td>
<td>Appearance of new lesions or progression of nontarget lesions</td>
<td>New lesions added to tumor burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confirmation required</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Neither partial response nor progressive disease</td>
<td></td>
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Endpoints in Immunotherapy Trials: Immune Response Criteria (irRC)

Wolchok et al. CCR 2009

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Endpoints in Immunotherapy Trials: Significance of Atypical Patterns of Response

There is a population of melanoma patients who have progressive disease per RECIST criteria but have better overall survival than patients who have both irRC and RECIST progression.

Hodi et al. JCO 2016
Endpoints in Radiation/Immunotherapy Trials: Correlative Endpoints

• Potential predictive biomarkers in patients treated with PD-1 / PD-L1 inhibitors
  – PD-L1 expression
  – tumor infiltrating lymphocytes
  – mutational burden

• The impact of radiation on these factors in human patients is uncertain

Stromal PD-L1 expression (red) in HPV+ SCC head-and-neck cancer
Radiation/Immunotherapy Trials: Treatment Parameters

• Preclinical data suggest:
  – radiation dose / fractionation is important
  – optimal timing of RT may vary in relation to immune agent used
  – improved synergy with certain combinations (e.g., RT+PD-1+CTLA-4)

• These and other treatment parameters should be evaluated in clinical trials

• Correlative studies can help determine the impact of these factors on expected outcomes
# Ongoing & Planned Radiation + Immunotherapy Trials

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Example</th>
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<tbody>
<tr>
<td>Adding immunotherapy to radiation standard of care approach</td>
<td>• Adding PD-1 inhibitor to definitive chemoradiation for SCCHN</td>
</tr>
<tr>
<td>Adding radiation to immunotherapy standard of care</td>
<td>• Adding targeted radiation to PD-1 inhibitor in metastatic melanoma, NSCLC, etc.</td>
</tr>
<tr>
<td>Exploring synergy observed in preclinical studies</td>
<td>• Using radiation + immunotherapy in poorly immunogenic tumors</td>
</tr>
<tr>
<td></td>
<td>• Combining radiation with novel immunotherapy combinations</td>
</tr>
<tr>
<td></td>
<td>• Evaluating radiation parameters</td>
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Radiation / Immunotherapy Trials

• ETCTN 10021
  “A Phase 2 Study of MEDI4736(durvalumab) and Tremelimumab Alone or in Combination with High or Low-Dose Radiation in Metastatic Colorectal and NSCLC”

  • Tests the combination of radiation, PD-L1 and CTLA-4 blockade
  • Randomizes patients to immunotherapy with or without radiation
  • Evaluates different radiation dose regimens
Summary

• Supported by preclinical rationale, an increasing number of prospective clinical trials are testing radiation-immunotherapy combinations

• Incorporation of novel response criteria and correlative studies can help examine the impact of radiation parameters such as site, dose, fractionation, etc. on anti-tumor immunity

• Radiation can play traditional (locoregional control, palliation) and potentially novel roles (abscopal effects, immune stimulation) when combined with immunotherapy, and data extends beyond synergy with PD-1 inhibitors