Targeted Drugs and Radiation: Are There Interactions? The Risk and the Reward

Paul W. Sperduto, MD, MPP, FASTRO

May 19, 2016
Leksell Gamma Knife Society Meeting
Amsterdam
Conflict of Interest

Grant support from Merck
Outline

1. Some Definitions
2. Some History
3. Examples of Risk of combining drugs & radiation
4. Examples of Reward of combining drugs & radiation
5. Current Clinical Trials
6. Conclusions
Definitions: The Risk

**DRIVL:** Delayed Radiation-Induced Vasculitic Leukoencephalopathy

**Drivel:** nonsense, rubbish, gibberish, garbage, childish, silly meaningless talk
Definition

**Treatment-Related Necrosis:** A more accurate term for late effects when patient receiving immunotherapy and radiation.

**Radiation Necrosis** We should stop using the term radiation necrosis when the patient receives immunotherapy and radiation.
Abscopal Effect: A rare phenomenon in which a tumor is irradiated or surgically resected and other untreated tumors shrink or resolve.

The word “abscopal” is derived from the Latin prefix “ab,” meaning “away from,” and the Greek word “scopos,” meaning “target.”
Some Definitions

Targeted Therapies:

- **EGFR+** drugs such as erlotinib & gefitinib
- **ALK+** drugs such as crizotinib
- **BRAF+** drugs vemurafinib and dabrafenib

**Immunotherapy:** treatment that uses certain parts of a person’s immune system to fight diseases such as cancer.

- **Anti-CTLA4** drugs such as Ipilimumab
- **Anti-PD1** drugs such as nivolumab & pembrolizumab

Now FDA approved in melanoma, NSCLC, renal cell carcinoma and SCCA of Head & Neck and soon in bladder and triple-negative breast cancer.
Some Definitions

Types of Immunotherapy: Immunotherapy encompasses several different treatment approaches, each of which has a distinct mechanism of action, and all of which are designed to boost or restore immune function in some manner.

1. THERAPEUTIC CANCER VACCINES
2. MONOCLONAL ANTIBODIES
3. CHECKPOINT INHIBITORS
4. CYTOKINES
Coley vs Ewings

William B. Coley: 1862-1936: noticed a tumor regression after a sarcoma patient developed a post-operative streptococcal infection. He found case reports by Louis Pasteur, Robert Koch and Emil von Behring who all had reported cancer regression after infection. So he injected streptococcus into inoperable cancer patients. Furthermore, he tested early radiation machines and concluded they were not curative.

James Ewing, 1866-1943, a contemporary, said your crazy and recommended systematic study of radiation therapy. Imagine the debate!
History of the Abscopal Effect

1953: Mole RH first described the abscopal effect.  
**Br J Radiol 1953;26:234-41**

1979: Stone HB, Peters LJ showed host immune capability effected radiocurability of murine fibrosarcoma.  
**JNCI 1979;63:1229-35**

1982-2016: Various case reports showing abscopal effect but many more in the SRS era

2004: Demaria/Formenti showed abscopal effect is immune mediated.  
**IJROBP 2004;58:862-70.**

2005: Demaria/Formenti hypothesized that with correct immunotherapy, the irradiated tumor could become an “in vivo vaccine”.  
**IJROBP 2005;63:655-66**
History of the Abscopal Effect

It has since been described in a variety of different tumors including melanoma, renal cell carcinoma and lymphomas.

It has been observed more frequently in recent years when technological advancements have allowed high dose/fraction radiation treatments such as stereotactic radiosurgery and stereotactic ablative radiotherapy (SABR)
Evidence of Risk from the Interaction of Drugs and Radiation
Because RTOG 9508 had shown a survival benefit in pts w multiple mets in the subset with NSCLC, some lunatic proposed a phase III, three-arm trial in patients with NSCLC and 1-3 brain metastases comparing whole brain radiation and stereotactic radiosurgery alone versus with Temozolomide versus with Erlotinib

**RTOG 0320: Schema**

- **Number of Metastases**
  - 1. One
  - 2. Two or Three

- **Extent of Extracranial Disease**
  - 1. None
  - 2. Present

**Randomize**

- Arm 1
  - WBRT + SRS

- Arm 2
  - WBRT + SRS + Temozolomide

- Arm 3
  - WBRT + SRS + Erlotinib
Risk of Drug-Radiation Interactions: RTOG 0320:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>MST (mo)</th>
<th>Grade 3-5 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT+SRS</td>
<td>44</td>
<td>13.4</td>
<td>11%</td>
</tr>
<tr>
<td>WBRT+SRS+Temodar</td>
<td>40</td>
<td>6.3</td>
<td>41%</td>
</tr>
<tr>
<td>WBRT+SRS+Erlotinib</td>
<td>41</td>
<td>6.1</td>
<td>49%</td>
</tr>
</tbody>
</table>

Sperduto, Int J Rad Onc Biol Phys 2013;85:1312-18
Risk of Drug-Radiation Interactions: BRAF Inhibitors & Radiation

Literature review of 27 articles showing increased dermatologic, pulmonary, neurologic, hepatic, esophageal and bowel toxicity in pts receiving BRAF inhibitors (vemurafenib and dabrafenib). 7 papers showed increased intracranial toxicity altho rate of necrosis and hemorrhage do not appear increased.

ECOG Guidelines for Avoiding Severe Toxicity: Hold RT for > 3 days before and after RT and > 1 day before and after SRS

Anker, IJROBP 2016;95(2):632-646  June 1, 2016
The Risk of Interaction Between Immunotherapy and Radiation

Alomari et al described two cases of patients with brain metastases (melanoma and NSCLC) who were treated with SRS followed by immunotherapy.

Both developed Delayed Radiation-Induced Vasculitic Leukoencephalopathy (DRIVL).

The Risk: Case 1

45 yo WF
2008: diagnosed w melanoma on her foot
2010: biopsy-proven BRAF+ inguinal adenopathy treated with one year of interferon
2011: developed lung and brain metastases, treated w GK for 5 brain mets and ipi, vemurafenib, carbo+taxol, dabrafenib, trametinib
2014: new 1.3cm right ant temp brain met rx’d w GK (22 Gy to 50% IDL).

5 mo after SRS she received pembro
1 mo after pembro she developed headaches and seizures.
MRI showed increased size of lesion and edema
Craniotomy: path= DRIVL
Re-started Pembro 2 wks after surgery
Brain MRI 3 mo after surgery was stable. Pt asymptomatic
MRI and Path showed:
The Risk: Case 1

A & B: T1 & Flair  
C & D: 2 mo after SRS  
E & F: 1 mo after pembro (6 mo after SRS)  
G & H: post-resection images showing mild residual flair
The Risk: Case 1

A & B: H&E stain shows necrotic tumor, melanin pigment & hemorrhage

C: H&E: necrotic tissue only

D & E: Brain tissue further from melanin nodule showing marked radiation-induced vascular wall thickening, hyalinization & lymphocyte infiltration

F: CD3 immunostain shows lymphocytic inflam infilt in vasculitic lesions
The Risk:  Case 2

59 WF smoker presents with confusion & speech difficulty.
Brain MRI:  left frontotemporal mass
Chest CT:  RUL mass w mediastinal lymphadenopathy
Lung Bx:  NSCLC (adenocarcinoma)
Brain Met rx’d w GK (20Gy to 50%IDL)
Brain MRI 1 mo later showed the lesion smaller -->  Nivo + Ipi started
2 mo after immunotherapy, imaging showed dramatic improvement in systemic disease but increase in edema & size of the brain met
   THIS MEANS INFLAMMATION IN THE BRAIN IS A MORE SERIOUS PROBLEM THAN IN EXTRACRANIAL SITES.
Craniotomy:  Path showed DRIVL
Resumed systemic therapy 2 wks after surgery.
Currently asymptomatic
MRI and Path showed:
The Risk: Case 2

A & B: T1 & Flair   C & D: 1 mo after SRS   E & F: 2 mo after nivo + ipi (3 mo after SRS)
G & H: post-resection images showing near total resection & markedly reduced flair signal
The Risk: Case 2

A & B: Mostly necrosis after SRS, minute tumor upper right

C: Immunostain shows small collection of tumor

D: H&E shows intense vasculitis w hyalinization of vessel walls & infiltration by inflammatory cells

E: CD3 immunostain shows T lymphocytes infilt vessel wall

F: CD68 immunostain shows macrophages & microglial cells infilt vessel walls & nearby brain
Imagine

What if you had treated 10 mets w SRS (because WBRT causes cognitive impairment) and got that degree of edema surrounding 10 lesions.

Could be fatal.

Caution
FDA Approval for Immunotherapy

Melanoma
NSCLC
Renal Cell Carcinoma
SCCA of the Head & Neck
Trials nearing completion
Bladder
triple-negative breast cancer others

Most cancer patients will get immunotherapy in the near future ➔ Risk ➔ CAUTION
Evidence of Reward
from the Interaction of
Immunotherapy and Radiation
The Reward: Cases 1-4; Examples of Abscopal Responses after Radiation and CTLA-4 Checkpoint Blockade

<table>
<thead>
<tr>
<th>Reference</th>
<th>Radiation</th>
<th>CTLA-4 Ab Dose</th>
<th>Tumor Type</th>
<th>Target</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dewan</td>
<td>6 Gy x 5</td>
<td>10mg/kg</td>
<td>Breast</td>
<td>Primary tumor</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>8 Gy x 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hiniker</td>
<td>18 Gy x 3</td>
<td>3mg/kg</td>
<td>Melanoma</td>
<td>Liver mets</td>
<td>Clinical</td>
</tr>
<tr>
<td>Postow</td>
<td>9.5 Gy x 3</td>
<td>10mg/kg</td>
<td>Melanoma</td>
<td>Paraspinal mets</td>
<td>Clinical</td>
</tr>
<tr>
<td>Golden</td>
<td>6 Gy x 5</td>
<td>3mg/kg</td>
<td>Lung cancer</td>
<td>Liver mets</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4

Hiniker, Translat Oncol 2012;5:404-7

Note: All radiation was hypo-fractionated SABR, not SRS
Evidence that SRS & Immunotherapy are Tolerable

Multiple reports show the combination of ipilimumab and SRS is well tolerated.

Knisely, J Neurosurg 2012
Silk, Cancer Medicine 2013
Shoukat, ASCO Annual Meeting, 2013
Tazi, Cancer Medicine 2015
Patel, Am J Clin Onc 2015
Kiess, Int J Rad Onc Biol Phys 2015
The Reward: Case 1

33yo WF
2004: mole on back excised, path=melanoma
2008: lung met -> biopsy + melanoma (BRAF-negative)
    -> chemo
2009: paraspinal mass & hilar adenopathy -> ipi 10mg/kg q 3 wk x 4 then maintenance q 12 wks
2010: slight progression
11/2010: right back pain
12/2010: SBRT 9.5 Gy x 3 in 7 days to para-spinal met
2/2011: one more dose of Ipi
4/2011: both irradiated and non-irradiated (Rt hilar & splenic mets) responded.

Postow NEJM 2012;366:925-31
Recurrence of Unresectable Cancer

Aug. 2009

August 2009

28.5 Gy/3 fractions

Recurrence of Unresectable Cancer

Induction  Maintenance  Radiation  Maintenance

Stable  Slow Progression  Response  Stable


Tumor shrinkage was associated with antibody responses to the antigen NY-ESO-1 & other antigens & an increase in CD4+ T cells in the peripheral blood

Postow 2012
Marker of T-cell Activation: Inducible Co-Stimulator (ICOS)
Myeloid Derived Suppressor Cells

![Graph showing the percentage of Myeloid Derived Suppressor Cells (MDSCs) over time. The graph includes a peak labeled Radiotherapy and shows fluctuations in MDSC levels from September 2009 to October 2011.](image-url)
The Reward: Case 2

History: 79yo WM w 70pk-yr smoking hx

2/15 abd pain: u/s shows rt renal mass-observed

8/15 confusion: Brain MRI shows two mets

9/14/15: craniotomy w resection of one met:
   path renal cell carcinoma

9/30/15: GK to other brain met

10/8/15: PET shows hypermetabolic rt renal mass

11/18/15: nephrectomy: no active tumor in primary lesion, just scarring and inflammation c/w regressed tumor

Abscopal effect due to surgery or GK or both
The Reward: Abscopal Example 2

A: Resected brain met shows renal cell CA

B: Nephrectomy after craniotomy & GK to second brain met shows no tumor in primary lesion
The Reward: Abscopal Example 3

Right inguinal adenopathy resolves 11 months after SRS for brain.

Doing well 1.5 years after SRS.

Sullivan et al. NEJM 2013
The 5\textsuperscript{th} R of Radiobiology

Golden & Formenti recently suggested \textit{Rejection} by immune response should join the classical four R’s of radiobiology

1. Reassortment
2. Reoxygenation
3. Repair of sublethal damage
4. Repopulation
5. Rejection by immune response

Golden & Formenti. Oncoimmunology 2014;3:e28133
But Many Questions Remain

1. What is the mechanism behind the abscopal effect?
2. How to best integrate radiation-induced immune enhancement with modern immunotherapies, while minimizing risk?
3. What are the optimal radiation technique, dose and fractionation?
4. SRS vs SABR?
5. Ablative vs Non-Ablative Doses
What radiation technique is best for immune enhancement?

Extracranial SRS & SABR can exclude normal tissues but also the draining lymph nodes.

Contrary to past paradigms when regional nodes were electively included.

For purposes of immune enhancement, these nodes need to be preserved intact and functional in order to mount an effective immune response.
What dose and fractionation is needed for optimal immune response?

Conventional Fractionation: Abscopal was rare.
SRS: Abscopal more common
SABR: Abscopal even more common

When combined with CTLA-4 blockade, pre-clinical and clinical data suggest that a multi-fraction regimen may be better than a single large dose.

It is not known whether this is true when radiation is combined with PD1 inhibitors.
What site is best to irradiate for optimal immune enhancement?

Multiple reports (Postow, Golden, Hiniker) demonstrated an abscopal effect when the radiation targeted a visceral lesion.

It is possible that the lack of advantage from the addition of ipilimumab to radiotherapy in a large prospective randomized trial of castration-resistant metastatic prostate cancer may be explained by the facts that a bone lesion (not a visceral metastasis) was treated and that a single dose of 8 Gy was used, not a multi-fraction scheme. Kwon, Lancet Oncology 2014;15:700-12
The aforementioned case reports of radiation and immunotherapy (both those with adverse results and those with good results) occurred with biologic doses that are less than ablative.

**CAUTION IS REQUIRED**

Prospective trials are needed to answer whether ablative or non-ablative doses are optimal.
Ablative vs Non-Ablative Doses?

Formenti’s group has shown with CTLA4 and transforming growth factor-beta (TGF-b) that fractionated regimens (hypofx ie SABR) are superior to large single dose at achieving immunization and resulted in gene expression consistent w better activation of immunologic pathways.

Vanpouille-Box & Formenti, Cancer Res 2015
What timing and sequence of immunotherapy and radiation?

One Hypothesis: integrating radiation as one of multiple components of a STAGED effort to immunize the patient against his or her tumor. In such an approach, the goal is PRIMING the immune system with certain agents (? GM-CSF) then concurrent non-ablative hypofractionated RT and immunotherapy may achieve optimal results.

Formenti. Oncology Journal 2015, May 15
Partial List of Current Clinical Trials

1. NCT-02085070: Yale: pembro alone for untreated brain metastases, no RT
2. NCT-02716948: Hopkins: nivo + SRS in melanoma with spine or brain mets
3. NCT-02320058: MSKCC: Ipi + nivo for melanoma brain metastases
4. NCT-02731729: MSKCC: Ipi vs Ipi + nivo in pts who have progressed or relapsed after PD1 inhibition (but without brain mets)
5. NRG-BN-1526: Pembro +/- SRS (15 Gy) in melanoma brain mets in pts who have not received PD1 inhibition.
Conclusions

1. Yes, there is most definitely interaction between immunotherapy drugs and radiation.

2. Multidisciplinary approach is more critical than ever before and must include immunologists.

3. First, do no harm: There is significant risk associated with combining immunotherapy and SRS: DRIVL could lead to rapid neurological decline and death especially with the trend to treating more mets with SRS to avoid WBRT.
Conclusions

4. Anecdotal evidence of reward: abscopal effects are being increasingly reported in patients treated with immunotherapy and radiation.

5. Need for prospective trials to learn how best to safely use radiation and immunotherapy to activate the immune system.

5. I recommend CAUTION beginning with a SRS dose de-escalation study when combined with immunotherapy. New NRG protocol will use 15 Gy.
7. Most of what we know about radiation dose & fractionation for brain metastases today is 
obsolete because immunotherapy changes everything and most patients will receive it.