Combining Radiation Therapy and Immunotherapy: A Paradigm Shift

VI CONGRESO ALATRO
Asociación Ibero Latinoamericana de Terapia Radiante Oncológica
Punta Cana, República Dominicana
Nov 8th, 2017

Ana Botero, MD
Radiation Oncology Department
Memorial Cancer Institute
Hollywood, Florida
VI CONGRESO ALATRO
Asociación Ibero Latinoamericana de Terapia Radiante Oncológica

5-8 de noviembre de 2017
Path Road

• Summarized Clinical Trials combining Immunotherapy and Radiation (IO+RT)
• To discuss considerations in RT+IO clinical design such as endpoints and response criteria
Impressive Advancements in Radiation Therapy Technology in the Past 100 years

1950’s
- Cobalt machine

1960’s
- Teletherapy

1970’s
- Linear Accelerators

1980’s
- 2D - CT scan
- 3D - CRT
- Chemotherapy concurrent
- IMRT
- RapidArc
- IGRT

1990’s
- SBRT

Goal: Increase local control and decrease side effects
Improvements in Radiation Therapy

• More precise target definition
• Correction for heterogeneity
• Better understanding of normal tissue tolerance
• Image-guided radiation therapy that minimizes normal tissue margins and reduces missed target
Ionizing Radiation

Historically, therapeutic application of the IR is based on:

- Its cytocidal power
- Ability to selectively target tumors

Radiation affects cancer patients survival:

- Improve LC of the tumor
- Decreasing systemic spread
Immunotherapy System

• The immune system plays a key role in controlling and eliminating multiple different types of malignancies (Immuno-surveillance)

• Attempts at directly activating the immune system with positive stimuli have had a limited efficacy

• Checkpoint blockade immunotherapy has revolutionized immunotherapy and oncology

• Radiation may promote key steps in the development of immune responses
Cells of the Immune System

Diagram showing the relationship between innate and adaptive immune cells.
Flow of the Immune Cells
Cancer Immunoediting

Dunn GP, Old LJ., Schreiber RD. Immunity 2004
QUESTION

What are the steps required to generate an antigen specific T-cell mediated immune response?
Steps to Generate a Cytotoxic Adaptive Immune Response

• Inflammation, antigen uptake and antigen-presenting cells (APC) maturation
• Migration to the lymph node and antigen processing and presentation
• T-cell priming and clonal expansion
• Cytotoxic effector response, tumor clearance and memory
Sequence of Steps of Cytotoxic Adaptive Immune Response

**STEP 1**
- Immature DC
- Antigen presentation
- DC maturation

**STEP 2**
- Antigen presentation
- MHCI
- CD4
- CD40L
- CD40
- TCR
- CD8
- IL-12
- INFγ
- T-cell expansion
- T-cell migration
- T-cell apoptosis

**STEP 3**
- NK cell
- CTL
- IL-12
- T-cell

**STEP 4**
- Prolonged CTL activity
- Myeloid-derived suppressor cell
- TREG
Step 1: Inflammation, Antigen Uptake and APC Maturation
Step 1: Inflammation, Antigen Uptake and APC Maturation

The Professional APC’s:

- Dendritic cells!
- Macrophages:
  - Langerhans cells
  - Microglia
  - Kupffer cells
  - Alveolar macrophages
- B cells

Radiation induces immune-mediated cell death and DC maturation

1) Radiation induces DAMPs which result in cross presentation by DCs
2) Radiation induces DAMPs which result in DC maturation

- Antigen capture by dendritic cells (DC)
- Loss of DC adhesiveness
Radiation Modifies Antitumor Immune Responses

- DNA damage and free oxygen radicals
- Inflammatory tumor cell death
- Activation of the damage-associated molecular patterns (high mobility group box chromosomal protein 1)
- HMGB1 activates antigen-presenting cells

Up regulation of major histocompatibility complexes (MHCs) increasing presentation of antigens on the surface of tumor cells
Step 2: Antigen Processing and Cross Presentation

Radiation enhances antigen cross presentation
Step 3: T-cell Priming and Clonal Expansion
Step 4: CD8 T-cell mediated Cytotoxicity

Two Main Mechanisms of T-cell mediated cell death:

1) FAS/L

Radiation induces FAS/FAS-L and upregulates MHC

2) Perforin and granzyme B

Radiation induces FAS and up regulates MHC

Radiation Modifies Antitumor Immune Responses

- Interleukin (IL)-1, IL-2, IL-6
- Tumor necrosis factor (TNF)-alpha
- Transforming growth factor (TGF)-beta
- Chemokine (C-X-C motif) ligand 16 (CXCL-16)
- Type I and type II interferon
T-cell mediated Cytotoxicity
Radiation Induced Immune Responses

Myth: “Radiation Is Immunosuppressive”

- Large radiation fields encompassing significant volumes of bone marrow or blood pool have been observed to result in decreases in white blood cell counts.
- SRBT significantly limiting the volume of bone marrow, thereby minimizing immunosuppressive effects.
- The advance in radiation technology calls for a re-evaluation of the effects of focused radiation on the immune system.
• Experimental data from cancer models have provided sufficient evidence to propose a paradigm shift, whereby the effects of the IR are recognized as contributing to the systemic antitumor immunity

• Traditional palliative role of RT in metastatic disease has evolved into a powerful adjuvant for immunotherapy

• IR has the capacity to convert irradiated tumor in situ, individualized vaccine
Potential Immune-stimulatory Effects of The SRS

- Increases permeability of the blood-brain barrier
- Increases immune cell infiltration
Potential Immune-Stimulatory Effects Of SBRT For Lung Cancer

• Activation of antigen-presenting cells
• Enhancement of the tumor antigen cross-presentation in the draining lymph nodes
• Activation and proliferation of tumor-specific cytotoxic T cells
In Vitro Assessment of Immunogenic Death Cell

Implications of Concurrent Chemo-RT

TS/A murine mammary tumor cells

Golden et al. Oncoimmunology
Strong Preclinical Trials

• Immunotherapy enhances the local effects of the radiation
• Radiotherapy potentiates the systemic effects of the immunotherapy:
  Abscopal (Out-field)
  Vaccine-like (In Situ)
Abscopal Effect
Imiquimod and RT

BIOLOGY CONTRIBUTION

IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

SANDRA DEMARIA, M.D.,* BRUCE NG, M.S.,† MARY LOUISE DEVITT, A.A.S.,‡ JAMES S. BAER, PH.D.,§ NORIKO KAWASHIMA, M.S.,* LEONARD LIEBES, PH.D.,| AND SILVIA C. FORMENTI, M.D.*

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York

Irradiated
don-n-irradiated

![Graphs showing tumor weight over days for irradiated and non-irradiated conditions with different treatment groups.](image-url)
Abscopal Effect
Imiquimod + RT

Follow up to Day 40
F/U

RT (Day 12, 13, 14)
Day 10, 12, 14
Day 17, 19, 21
Day 24
IMQ

Primary tumor IMQ

RT

Day 0
Inj. of TSA
$10^5$ cells sc Rt.

Tumor volume (mm$^3$) ± SEM

- PLA+0Gy
- IMQ+0Gy
- PLA+8Gy x 3
- PLA+8Gy x 3

Day 26
Day 39

PLA+0 Gy
IMQ+0 Gy
PLA+8 Gy x 3
IMQ+8 Gy x 3
Abscopal Effect

Completed Trials: RT + Systemic GM-CSF
Golden et al. Lancet Oncology 2015

- Stable or progressing solid tumors treated with 35 Gy in 10 fractions and systemic GM-CSF

- Endpoint: abscopal responses
  - defined as 30% decrease in non-irradiated lesions

Above: Abscopal responses observed in 11 of 41 patients

Granulocyte Macrophage Colony-Stimulating Factor - Leukine
Abscopal Effect
Increased OS

26.8% abscopal responses

Median OS: 20.98 versus 8.33 months
Abscopal Effect
In Situ Vaccination with TLR9 Induces Systemic Lymphoma Regression (Phase I/II)

Patient A:
treated at occipital lesion, response in bilateral axilla.

Patient B:
treated at suprasternal cutaneous lesion, response at frontal lesion
Abscopal Effect

RT + TLR7 agonist Imiquimod: abscopal response
Abscopal Effect
Abraxane and PDL-1 Blockade

Low dose CTX, IMQ and RT (6 Gy X 5) in metastatic TNBC
Preclinical trial experiences suggest synergy for radiation and checkpoints
Metastatic melanoma patients
SBRT and Ipilimumab
Heavy Ions Therapy
Protons, Deutrons and Alpha Particles

- Radiological Research Accelerator Facility (RARAF) at Columbia University
- Experimental irradiation using the Track Segment Charged-Particle Accelerator
- Allows for irradiation of particles of varying Linear Energy Transfer

<table>
<thead>
<tr>
<th>Particle</th>
<th>LET Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>8-60 keV/µm</td>
</tr>
<tr>
<td>Deuteron</td>
<td>20-70 keV/µm</td>
</tr>
<tr>
<td>Helium-3</td>
<td>50-110 keV/µm</td>
</tr>
<tr>
<td>Helium-4</td>
<td>80-200 keV/µm</td>
</tr>
</tbody>
</table>
• Radiation is an optimal partner for immunotherapy: strategies to enhance cross-priming enable the abscopal effect

• Hypo-fractionated, short courses of RT to a small target to avoid lymphopenia are preferable.

• IL-15 may enhance RT pro-immunogenic effects.

• Preliminary evidence suggest that heavy ions may induce more ICD and be optimal partners with immunotherapy*

*VI CONGRESO ALATRO
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 2018
Promising preclinical and anecdotal data has led to the 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
Promising preclinical and anecdotal data has led to the development of numerous RT+IO trials

- Johnson and Jagsi IJROBP 2016: 81 ongoing trials testing radiation-immunotherapy combinations
- What can we learn from completed RT+IO trials?
- What are important aspects of trial design unique to IO combinations?
Completed Trials RT + Ipilimumab
Trend to increase OS

- 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, RT dose/fractionation/site, ipilimumab dose

Know et al. Lancet Oncology 2014
End Points for the New Clinical Trials
(Based on lessons from the preclinical trials)

• Abscopal effect
• Response vs. Survival
• Biological effect
• To evaluate a RT/IO isolate component effects: RT timing, total dose/fractionation, site and IO agent
• Safety
Endpoints in Immunotherapy Trials: Safety Endpoints

- A spectrum of immune-related adverse events has been observed with immune checkpoint inhibition
- Prompt diagnosis and treatment are critical
- Early data suggest that focal RT + immune checkpoint inhibitors are well tolerated (Barker et al. CIR 2013, Wilhite et al. AACR 2016)
Endpoints in Immunotherapy Trials: Atypical Patterns of Response on CTLA-4 blockade

A: Response after treatment

B: “Stable disease” with slow decrease in tumor volume

C: Response after initial increase in tumor volume

D: Shrinking target lesions in the setting of new lesions that then regress

* 10% of patients characterized as having PD on initial ipilimumab trials ultimately had evidence of response

Wolchok et al. CCR 2009
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) and Immune RECIST (irRECIST)

**Immune-related response criteria (irRC):**
- Based on WHO criteria: measuring sum of products of 2 largest perpendicular diameters (SPD) of target lesions
- New lesions are incorporated into tumor burden (not automatic progression) – can be present in cases of partial response
- Progressive disease must be confirmed with scan >4 weeks after first scan

**irRECIST:**
- Uses unidirectional, longest diameter measurements
- Requires confirmation of progression
- New lesions don’t automatically constitute progressive disease
- % changes highly concordant with irRC (Spearman r=0.953-0.965)
- Unidirectional measurements more reproducible

Wolchok et al. CCR 2009 and Nishino et al. CCR 2013
Endpoints in Immunotherapy Trials: Immune-Related Response Criteria (irRC) Compared with Immune RECIST (irRECIST)

<table>
<thead>
<tr>
<th></th>
<th>Bidimensional assessment (the original irRC (7))</th>
<th>Unidimensional assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurable lesions</td>
<td>≥5 × 5 mm$^2$ by bidimensional measurements</td>
<td>≥10 mm in the longest diameter</td>
</tr>
<tr>
<td>Measurement of each lesion</td>
<td>The longest diameter × the longest perpendicular diameter (cm$^2$)</td>
<td>The longest diameter (cm)</td>
</tr>
<tr>
<td>The sum of the measurements</td>
<td>The sum of the bidimensional measurements of all target lesions and new lesions if any</td>
<td>The sum of the longest diameters of all target lesions and new lesions if any</td>
</tr>
<tr>
<td>Response assessment</td>
<td>PD: ≥25% increase from the nadir</td>
<td>PD: ≥20% increase from the nadir</td>
</tr>
<tr>
<td></td>
<td>PR: ≥50% decrease from baseline</td>
<td>PR: ≥30% decrease from baseline</td>
</tr>
<tr>
<td></td>
<td>CR: Disappearance of all lesions</td>
<td>CR: Disappearance of all lesions</td>
</tr>
<tr>
<td>New lesions</td>
<td>The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.</td>
<td></td>
</tr>
<tr>
<td>Confirmation</td>
<td>Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD</td>
<td></td>
</tr>
</tbody>
</table>

Nishino et al. CCR 2C
Radiation/Immunotherapy Trials: Evaluating 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
Atezolizumab (Tecentriq) humanized monoclonal antibody IgG isotype against PD-L1 for solid tumors.

- FDA approved 10/2016 for metastatic NSCLC progressing on platinum systemic therapy
Radiation/Immunotherapy Trials: Evaluating Treatment Parameters, Radiation Dose and Mechanisms of Action

Metastatic NSCLC that failed to respond to prior PD-1 or PD-L1 inhibitor

- Biopsy

- 8Gy x 3 + durvalumab/tremelimumab
- Low-dose RT* + durvalumab/tremelimumab

Continue durvalumab to progression

Optional biopsy - after cycle 2 - at progression

ORR PFS, Safety Correlative Endpoints

CTEP # 10021
SBRT and Immunotherapy
Timing and Dose

![Graph showing the number of HA-specific CD8^+ T cells at different doses of radiation.](image)

- *P<0.05
- *P<0.05
NRG ONCOLOGY

NRG-BR002

A Phase II/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

SCHEMA (9/16/16)

PATIENT POPULATION
Patients with locally controlled metastatic breast cancer with the following number of allowable metastases:
- \( \leq 4 \) metastases seen on standard imaging within 60 days prior to registration when all metastatic disease is located within the following sites: peripheral lung; osseous (bone); spine
- \( \leq 2 \) metastases seen on standard imaging within 60 days prior to registration when any one metastasis is located in one of the following sites: liver; central lung; mediastinal/cervical lymph node; abdominal-pelvic metastases (lymph node/adrenal gland)
and at least 1 pathologically confirmed visualized on CT or PET/CT.

STRATIFICATION
- Number of metastases (1 vs. > 1)
- Hormone receptor status (ER and/or PR positive vs. ER and PR negative)
- HER2 status (Positive vs. Negative)
- First-line standard systemic chemotherapy (Yes vs. No)

RANDOMIZATION

Arm 1
Standard of care systemic therapy\(^{a,b}\)

Arm 2
- Standard of care systemic therapy\(^a\)
- Ablation of all metastases (SBRT or surgery ablation)\(^c\)
Summary

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

• These studies should be informed by previous studies and data that suggest that unique response criteria are needed in immunotherapy trials

• There is a need for studies that evaluate the biologic and clinical effect of radiation parameters when used in combination with immunotherapy
Gracias por su atención!