Radiation Therapy and Immunotherapy: New Frontiers

May 12th, 2017
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Objectives

• Review concepts of radiation therapy treatment and techniques
• Overview of pre-clinical evidence of radiotherapy immunogenic effects
• Describe rationale for combination therapy and review evidence
• Review evidence of combination therapy
• Briefly review on-going trials investigating combination therapies
Stereotactic Body Radiation Therapy (SBRT)

• A paradigm shift in how radiation therapy is delivered over past decade
• Stereotactically localized, high dose RT
• Typical doses range from 30-60 Gy in 3-8 fractions
• Demands greater technical considerations
  • Tumor motion, immobilization, image guidance

Higher biologically effective dose = effective ablation of tumor
Systemic/local immune enhancement
- Vaccine
- Checkpoint inhibitors
  - Anti-CTLA-4
  - Anti-PD-1
  - Anti-TIM3
- Co-stimulatory agonists
  - Anti-OX40
  - Anti-4-1BB
  - Anti-CD27
- Anti-GITR
- Exogenous cytokines
  - IL-2
  - IL-7
  - IL-12
  - GM-CSF

Immune induction
- Cell death
- Necrosis

Primary tumour
- Radiation

Cell death
- Apoptotic bodies
- Debris
- Danger signals
- DAMPs
- TAAs
- Cytokines

Immune induction
- Dendritic cell cross-presentation of TAAs

Lymph node
- Vascular normalization

Distant tumour
- TAA-specific T cells

Vascular normalization
- Immune infiltration
- Immunogenic modulation
- Phenotype changes
  - T MHC
  - T TAA
  - T T-cell killing

Phenotype changes
- Polyvalent antigen-specific T cells
- Immuno-therapy
RT Alone: Preclinical Evidence

• SBRT elicits CD8+ T-cell immune response resulting in primary and metastatic tumor shrinkage or eradication in mouse models (Lee et al. Blood 2009)
  • Conventional fractionation not able to elicit similar response

• Other studies have demonstrated similar findings on facilitation of antigen presentation, priming of peripheral T-cells, and infiltration of tumor antigen specific T-cells.
RT Alone: Preclinical Evidence

- Data suggests a complex fractionation and dose-dependent relationship
  - **Threshold dose** below which immune stimulation suboptimal
  - **Ceiling dose** above which immunosuppression may prevail
  - Dose may impact the longevity of immune response

Bernstein et al *Cancer Bioherm. Radipharm.* 2014
Combination Therapy: Preclinical Evidence

- **Immunostimulatory Pathway**
  - anti-CD137; anti-CD40

- **Immunosuppressive Pathway**
  - RT and CTLA-4 blockade; RT and PD1 blockade
    - Mediated by CD8+ T-cell antitumor activity
    - Hypofractionated regimens may be superior to single fx regimen
    - RT enriched immune effector cells

- Combination of immunomodulators may be superior
  - Various mechanisms (exhaustion, etc.)
Clinical Evidence

- Retrospective
- Primarily in melanoma patients
  - Primarily ipi
  - Improved survival in patients receiving ipi and SRS for brain metastases vs. WBRT
- Case reports in NSCLC
  - Mainly ipi related
  - Intent of therapy in case report to generate abscopal effect
- Limited conclusions to be drawn except proof-of-principle
  - Differences in treatment sequencing, RT doses, location of response

Ongoing Trials

- Some investigating in melanoma only
- Others enrolling varying solid tumor types
- Newer studies investigating anti-PD1 agents or combination therapy

Patients with NSCLC, no prior PD-1 therapy

MK-3475 200 mg every 3 weeks
re-staging every 6 weeks
until progression

Progression of Disease

SBRT to a single lesion
Arm A: dose escalation for lung targets
Arm B: dose escalation for non-lung targets

MK-3475 200 mg every 3 weeks
re-staging every 6 weeks
until progression

Progression of Disease
OR unacceptable treatment-related toxicity
OR 1 year

Off study, post-treatment assessment

Patients with Melanoma,
Previously treated, with irPD
Phase 2a

Arm A: Patients with NSCLC, no prior PD-1 therapy
MK-3475 200 mg every 3 weeks re-staging every 6 weeks until progression
Progression of Disease
SBRT to a single lesion (at MTD)
MK-3475 200 mg every 3 weeks re-staging every 6 weeks until progression
Progression of Disease OR unacceptable treatment-related toxicity OR 1 year
Off study, post-treatment assessment

Arm B: Patients with Melanoma, Previously treated, with irPD
A RANDOMIZED DOUBLE-BLIND PHASE 3 STUDY OF AVELUMAB IN COMBINATION WITH STANDARD OF CARE CHEMORADIOThERAPY (CISPLATIN PLUS DEFINITIVE RADIATION THERAPY) VERSUS STANDARD OF CARE CHEMORADIOThERAPY IN THE FRONT-LINE TREATMENT OF PATIENTS WITH LOCALLy ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Randomized Double-Blind 2-Arm Study

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<thead>
<tr>
<th>Lead-in Phase</th>
<th>CRT Phase</th>
<th>Maintenance Phase$^d$</th>
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<tbody>
<tr>
<td>Avelumab 10 mg/kg IV$^b$ + SOC Chemoradiation$^c$</td>
<td>Avelumab 10 mg/kg IV$^b$</td>
<td>Avelumab 10 mg/kg IV Q2W</td>
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<tr>
<td>Placebo IV$^b$ + SOC Chemoradiation$^c$</td>
<td>Placebo IV$^b$</td>
<td>Placebo IV Q2W</td>
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N=640 LA SCCHN patients$^d$

1:1 randomization$^b$

Treatment until:
- Confirmed PD$^e$
- Patient withdrawal
- Lost to follow-up
- Unacceptable toxicity
- Study terminated by Sponsor
Future Directions

• **Potential Role in Early Stage Lung CA**
  • SBRT/SABR already viable alternative to curative surgical resection
  • Neither demonstrates significant impact on nodal (~5%) or distant (~10%) relapse
  • Potential advantage of combined therapy with curative intent SBRT and alternate role as in-situ tumor vaccine with immunotherapy

• **Role in Locally Advanced Disease?**
Summary

• **Productive interaction between stereotactic radiation and immune system, can be exploited**

• **Dose per treatment / fraction of radiotherapy matters**
  - Multiple fraction therapy may have benefits over single fraction therapy

• **Resistance to immunoradiotherapy combinations likely through non-redundant immune pathways**
  - RT/anti-CTLA4 -> antitumor CD8+ T-cell exhaustion via PD1 pathway
Summary

• **Optimal sequencing of therapy unknown**
  • Seemingly limitless combinations of therapy and sequencing

• **Endpoints matter**
  • PDL1 expression
  • CD8+ T-cell:T reg; CD8/CD4
  • Exome and proteosome analysis

• **Role for big data to accelerate hypotheses on optimal sequencing**
Thank You! Questions?