RBEs for Human Cancer Cells Exposed to Protons and Heavier Ions: Implications for Clinical Use of Charged Particles in Cancer Therapy

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Disclosures

No Conflicts

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RBEs of Human Cancer Cells

• Overview: Biological advantages of charged particles
• Quantification of RBEs for human tumors
• Role of genetic background on RBEs
• Hypofractionation
Why Charged Particles?

• Dose distribution advantage of protons and heavier ions
  – More dose in tumor while sparing normal tissues

• Biological advantages of heavier ions
  – Increased (tumor) cell killing
  – Decreased repair between fractions
  – Decreased effect of hypoxia

Increased Cell Killing with Heavy Ions

![Graph showing increased cell killing with heavy ions](image)

(from W. Kraft-Weyrather et al., Int. J. Radiat. Biol. 1999)

Increased Cell Killing:
Charged Particle Tracks Through DNA

![Image showing DNA damage and repair](image)

More complex DNA lesions, less repair (and less accurate repair), greater lethality.
Optimum Cell Killing (RBE) at ~100 keV/μm

RBE = Relative Biological Effect (ratio of dose for effect with photons to dose for same effect with ions)

Greater Relative Biological Dose in Tumors over Normal Tissues Can Yield a Therapeutic Gain

Why Charged Particles?

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**Hypoxic Cells are Resistant to Photons, but Hypoxic Resistance is Decreased with Heavy Ions**
Maximal Loss of Hypoxic Resistance at ~100 keV/\mu m

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Heavy Ion RBEs: "Classic" Biology

- RBE is highly complex: depends on LET, ion species, dose, dose rate/fractionation, tissue/cell type, endpoint, oxygen concentration, microenvironment (and almost anything else you can think of!)
Carbon Ion RBEs: Survival Curves with Human Cells

- Ando and Kase (2009): ~ 40 curves, mostly for human tumors; 3 for human fibroblasts

- Suit et al. (2010) – some of same studies as previous slide

Conclusion from cell survival curves: Little evidence to support idea of consistently different RBEs for normal tissues than for tumors (if you think fibroblasts represent normal tissues).

RBE vs LET for Human Tumor Cells: Various Parameters from Survival Curves (Literature Summary)

Large spread in RBE values at any given LET.
RBE$_{10}$ vs LET for Human Tumor Cells: Various Charged Particles

Note the effectiveness of helium ions

Our Recent Studies at NASA Space Radiation Laboratory (NSRL) at Brookhaven National Lab (BNL)

Horizontal stack of water/media-filled T25 flasks containing cells aligned along beam axis; varying thicknesses of tissue equivalent polyethylene in front.

In physics measurements, Bragg peak at ~ 22.5 cm (surface of 10th flask in stack)

“Inverse” Bragg Curve with Human Cells: 355 MeV/n Carbon Ions

Surviving Fraction
RBE (10% survival) Values (relative to 250 kVp X-rays) for Human Cells

<table>
<thead>
<tr>
<th>Species</th>
<th>carbon (355 MeV/n)</th>
<th>Oxygen (430 MeV/n)</th>
<th>Helium (190 MeV/n)</th>
<th>Lithium (215 MeV/n)</th>
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*RBE values in () were estimated from extrapolation of data available only at higher survival levels. --- indicates insufficient data even to extrapolate.
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**Some NSCLC Cell Lines Have Proton RBE > 1.1**

H. Willers collaboration
Some NSCLC Cell Lines Have Proton RBE > 1.1

Cell Lines with Higher Proton RBEs May Be Defective In DNA Repair

Cell Lines Defective in BRCA1 or Fanconi Anemia Pathway Are Sensitive to Protons
Identification of Patients Whose Tumors are More Sensitive to Charged Particles

• Could guide selection of patients whose tumors might be treated more effectively with particles.
• Might allow de-escalation of charged particle dose if normal tissues of concern.
• Could facilitate use of biologically optimized tumor-directed therapy to improve tumor control.

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Clinical Trend with Carbon Ion Therapy Is To Hypofractionation

Examples of treatments at NIRS (Kamada et al. 2015)
• In peripheral stage I NSCLC, number of fractions reduced from 18 to 9 to 4 to 1.
• Prostate cancer treated in 16 fractions over 4 weeks, now reduced to 12 fractions over 3 weeks.
• In different protocols, hepatocellular carcinoma treated with 4 fractions or 2 fractions over 2 weeks.
• Pancreatic cancer treated with 12 fractions over 3 weeks.
Experimental Data on RBEs with Fractionated Heavy Ions Are Limited

Growth delay in NFSa tumor and skin reactions after carbon ion irradiation
(from Ando et al. 2005)

![Graph showing growth delay in NFSa tumor and skin reactions after carbon ion irradiation.](image)

Carbon Ion RBEs for a Prostate Tumor

![Graph showing carbon ion RBEs for a prostate tumor.](image)

Decreasing Number of Fractions (increasing dose/fraction) with Charged Particles

- Will measuring more RBE values in experimental systems help treat patients?
- Changing two parameters at once:
  - Fractionation
  - LET

- What’s the Biology?
Is Hypofractionation with Carbon Ions “Just” More Dose or “Different” Dose?

![Graph showing dose vs. probability with different symbols for Phocea, Proneva, and Carbon Ions.](from Luedth and Durante 2013)

**Decreasing Fraction Number with Ions**

**What’s the Biology?**

- 4 (5) R’s
  - Repopulation
  - Redistribution
  - Reoxygenation
  - Repair
  - **(Inherent Radiosensitivity)**

- “New” biology

Are “R”s Important?

<table>
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<tr>
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<th>Conventional photons</th>
<th>Hypofractionation photons</th>
<th>Carbon Ions</th>
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<tbody>
<tr>
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<td>yes</td>
<td>no</td>
<td>less?</td>
</tr>
<tr>
<td>Redistribution</td>
<td>maybe</td>
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<td>little</td>
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<tr>
<td>Reoxygenation</td>
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<td>no</td>
<td>maybe less</td>
</tr>
<tr>
<td>Repair</td>
<td>yes</td>
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Molecular Mechanisms: Uniqueness of Track Structure

Slower and less complete repair of DNA damage from carbon ions

DNA repair following protons or $^{12}$C requires homologous recombination

sRNA knockdown on FANCD2 (and others)

HR inhibitor

Decreasing Fraction Number with Ions

What’s the Biology?

- 4 (5) R’s
- “New” (different) biology – high dose or high LET?
  - More apoptosis
  - Damage to vasculature
  - Changes in reoxygenation
  - Immune effects
  - More killing of cancer stem cells
  - Changes in tumor cell migration
  - Suppression of angiogenesis factors
  - Altered gene expression patterns
  - Altered intra- and inter-cellular signaling
Some Data Suggest High Doses Increase Vascular Damage

- Kolesnick, Fuks et al. have shown substantial radiation-induced apoptosis in tumor endothelial cells.

Reoxygenation Can Be Different after Carbon Ions in Some Tumors

- Reoxygenation can be different after carbon ions in some tumors.

High Doses May Increase Immune System Effects on Tumor

- In some systems reduction of tumor burden after ablative RT depends largely on T-cell response.
Decreasing Fraction Number with Ions

What’s the Biology?

• 5 R’s
• “New” (different) biology – high dose or high LET?
  – More apoptosis (both but maybe different cell types)
  – Damage to vasculature (both)
  – Faster reoxygenation (maybe both, but LET more)
  – Immune effects (both, but LET more)
  – More killing of cancer stem cells (LET)
  – Tumor cell migration (inhibited with high LET)
  – Angiogenesis factors (suppressed with high LET)
  – Altered gene expression patterns (both, but different)
  – Altered intra- and inter-cellular signaling (both, but different)

Summary

• Biological advantages of ions heavier than protons include increased cell killing, decreased repair, and decreased OER.
• RBE values depend on many, many factors; differences between tumors and normal tissues not clearly evident, although normal tissue data are limited.
• How high are RBE values beyond the Bragg peak?
• Are helium ions useful?
• Genetics, especially of tumors, may be useful to exploit.
• Hypofractionation of ions is increasing, but biology is less understood and may involve complex interplay of “different” biology at high doses and with high LET.

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THANK YOU