A Novel Radiosensitizing Agent for the Treatment of Chordoma

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Disclosures

• Experimental use in animal models

• No human subjects

• Not currently FDA approved for any indication

Learning Objectives

• Describe current management strategies for intracranial chordoma and cite potential mechanisms of therapeutic resistance

• Explain how effectiveness of radiation therapy can be influenced by tumor cell cycle and DNA repair mechanisms

• Understand relevance of protein phosphatase 2a (PP2a) inhibition and potential role in combination with radiotherapy

Epidemiology

• 300 cases/year

• Intracranial chordoma survival
  – 5-year: 63%
  – 10-year: 16%

**Biology**

- Low grade
  - Locally aggressive
- Notochord remnant

**Location** = axial skeleton
- Clivus (32%)
- Spine (32.8%)
- Sacrum (29.2%)


**Current Management Strategies:**

**Surgery**

- Radical (vs. incomplete) resection most important predictor of survival ($p < 0.001$)

- Endoscopic (vs. open) approach achieved complete resection more often (61 vs. 48%; $p=0.010$) with less morbidity

Current Management Strategies:

**Radiation Therapy (1/3)**

- RT commonly used for following cases:
  - Recurrence
  - Incomplete resection
  - “Unresectable” tumor

- Dose-response relationship above effective dose of 65 Gy

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Current Management Strategies: Radiation Therapy (2/3)

- Radioresistant tumor
  - Proximity to critical neuroanatomy
- Proton beam radiotherapy (PBRT):
  - Precise, high dose can be administered


Current Management Strategies: Radiation Therapy (3/3)

- PBRT (vs. Conventional RT): prolonged recurrence-free survival
  - 4-year RFS: 91 vs. 19%
- Severe toxicity seen with doses >72 CGE (standard dosing)


Current Management Strategies: Unmet Need

- Reduce effective dose of RT needed in order to preserve function of healthy surrounding neuroanatomy
  - (aka “radiosensitize” chordoma cells)
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Table 1: Cell-cycle distribution and DNA contents of the three cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>G1 phase</th>
<th>S phase</th>
<th>G2/M phase</th>
<th>DNA content</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-CH1</td>
<td>22.5%</td>
<td>17.0%</td>
<td>60.5%</td>
<td>2.0x normal</td>
</tr>
<tr>
<td>U-CH1 (h)</td>
<td>64.0%</td>
<td>21.0%</td>
<td>15.0%</td>
<td>2.0x normal</td>
</tr>
</tbody>
</table>

Note: Cells were treated with X-rays at a dose of 0.5 Gy and harvested at 48 hours. Means with a standard DNA content in normal control (2.0x normal) are indicated in italics.

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**LB100: novel inhibitor of PP2a**

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Study Aims

• Evaluate efficacy of combination LB100 and radiotherapy against chordoma in vitro.

• Identify mechanisms responsible for hypothesized increase in radiosensitivity.

Methods

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>UCH-1; UCH-2 Human chordoma cell lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>LB100 administered 3h prior to RT</td>
</tr>
<tr>
<td>Radiation</td>
<td>3.09 Gy/min Cesium-source irradiator</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Cell Counting (Trypan blue)</td>
</tr>
<tr>
<td>Cell cycle analysis</td>
<td>FACS (Flow cytometry)</td>
</tr>
<tr>
<td>DNA repair</td>
<td>Immunofluorescence microscopy</td>
</tr>
</tbody>
</table>
Results:
LB100 enhances cytotoxic effect of radiation in vitro

Results:
LB100 lifts cell cycle arrest and increases percentage of cells in G2/M phase

Results:
LB100 inhibits cellular repair of dsDNA breaks after radiation
Conclusions:
• Surgery +/- Adjuvant RT
  – Mainstays of treatment for intracranial chordoma
• Dose limiting toxicities
  – Need for radiosensitization of tumor cells
• PP2a can increase RT effectiveness via:
  – Increasing % of tumor cells in G2/M (radiosensitive) phase of cell cycle
  – Preventing tumor cell from repairing DNA damage induced by RT

Current / Future Directions:
• Animal studies
  – Subcutaneous flank model (IL2Rg null mice)
• Phase I Clinical Study (complete)
  – LB100: Safe for use in humans
  – Phase II study to evaluate efficacy in chordoma

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