T Cell Immunotherapy - Optimizing Trial Design

Office of Biotechnology Activities

September 10, 2013

Host preparation

Steven A. Rosenberg, M.D., Ph.D.
Surgery Branch, National Cancer Institute
Mechanisms Underlying the Impact of Lymphodepletion on Adoptively Transferred T Cells

- Eliminate cytokine sinks
- Eradicate regulatory elements
- Enhance APC activation & availability
HOST LYMPHODEPLETION PROFOUNDLY ENHANCES THE ANTITUMOR EFFECT OF ADOPTIVELY TRANSFERRED CELLS IN MOUSE MODELS

1. Effect is on the host – not the tumor

2. Elimination of T regulatory cells

3. Elimination of lymphocytes that are cytokine “sinks” (T cells and NK cells)

4. Host IL-7 and IL-15 are essential

5. Activation of host antigen presenting cells are critical (antibiotics partially impair effect of TBI)
Direct Correlation Between the Amount of Irradiation and the Anti-tumor Effect
Addition of T Regulatory Cells Damages the Treatment Impact of Adoptively Transferred Cells

![Graph showing tumor area over days post treatment with different treatments: No Treatment, PF, PFI CD4+CD25+, and PFI. The y-axis represents tumor area in mm², and the x-axis represents days post treatment.]
Increased access to supportive endogenous cytokines in irradiated hosts enhances anti-tumor efficacy of transferred T cells.

Treatment is impaired in irradiated mice genetically deficient in IL-15 or IL-7 and IL-15 vs. WT mice. Mice bearing 9-day-old established subcutaneous B16 tumors were treated with adoptive transfer of pmel-1 T cells with vaccine and rhIL-2, with or without TBI.
Sublethal Irradiation Acts on the Host – Not the Tumor

Graph (a): Tumor area (mm²) vs. Days post treatment for different treatments:
- No treatment
- 5Gy on tumor
- 10Gy on tumor
- 20Gy on tumor

Graph (b): Tumor area (mm²) vs. Days post treatment for different treatments:
- Treatment
- 5Gy TBI + Treatment
- 5Gy TBI (tumor shield) + Treatment
- Treatment + 5Gy on tumor
Integrating Preparative Nonmyeloablative Chemotherapy With Adoptive T-Cell Transfer

Cytoxan and Fludarabine

TIL Transfer

IL-2

Days to cells

cells/mm3
<table>
<thead>
<tr>
<th>Days</th>
<th>-7</th>
<th>-6</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>Cy</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Cells</td>
<td>IL-2</td>
<td>IL-2</td>
<td>IL-2</td>
</tr>
<tr>
<td>Ablative (200cGy)</td>
<td>Cy</td>
<td>Flu</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>TBI</td>
<td>Cells</td>
<td>IL-2</td>
<td>IL-2</td>
</tr>
<tr>
<td></td>
<td>CD34+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablative (1200cGy)</td>
<td>Cy</td>
<td>Flu</td>
<td>Cy</td>
<td>Flu</td>
<td>Flu</td>
<td>Flu</td>
<td>TBI</td>
<td>TBI</td>
<td>TBI</td>
<td>Cells</td>
<td>IL-2</td>
</tr>
<tr>
<td></td>
<td>CD34+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Total</td>
<td>PR</td>
<td>CR</td>
<td>OR (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>--------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>number of patients (duration in months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No TBI</td>
<td>43</td>
<td>16 (37%)</td>
<td>5 (12%)</td>
<td>21 (49%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 4, 4, 2, 2)</td>
<td>(114+, 112+, 111+, 97+, 86+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 TBI</td>
<td>25</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
<td>13 (52%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(14, 9, 6, 6, 5, 4, 3, 3)</td>
<td>(101+, 98+, 93+, 90+, 70+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200 TBI</td>
<td>25</td>
<td>8 (32%)</td>
<td>10 (40%)</td>
<td>18(72%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(21, 13, 7, 6, 6, 5, 3, 2)</td>
<td>(81+, 78+, 77+, 72+, 72+, 71+, 71+, 70+, 70+, 70+, 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(20 complete responses: 19 ongoing at 70 to 114 months)
Randomized NMA vs NMA-TBI Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>PR</th>
<th>CR</th>
<th>OR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMA</td>
<td>44</td>
<td>16 (36%)</td>
<td>5 (11%)</td>
<td>21 (48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26+, 19, 19+, 18+, 17+, 17+, 17+, 16+, 14+, 12+, 11+, 7, 7+, 6, 4, 3+</td>
<td>23+, 19+, 16+, 15+, 10+</td>
<td></td>
</tr>
<tr>
<td>NMA-TBI</td>
<td>42</td>
<td>23 (55%)</td>
<td>3 (7%)</td>
<td>26 (62%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26+, 25, 25+, 21+, 20+, 19+, 17+, 16+, 16+, 13, 12+, 11+, 9, 9, 8, 8+, 7+, 6, 5, 5+, 4, 4+, 4+</td>
<td>27+, 23+, 22+</td>
<td></td>
</tr>
</tbody>
</table>

(8 complete responses: 8 ongoing at 10 to 27 months)

(1ST patient randomized 3/24/11)

(Simultaneous TIL trial no IL-2; 2 of 16 (13%) ongoing responses.)
Recovery of neutrophils after ACT using a lymphodepleting regimen
Recovery of lymphocytes after ACT using a lymphodepleting regimen
Impact of Lymphodepletion on Serum Levels of IL-15 and IL-7
(As of 1/2/08)

No TBI

200 TBI

1200 TBI

pg/ml IL-15

pg/ml IL-7

Pre Day 0

Pre Day 0

Pre Day 0
M. M.
1200 TBI + TIL + HD IL-2, Prior IL-2

W.K.
1200 TBI + TIL + HD IL-2, Prior IL-2

L.R.
1200 TBI + TIL + HD IL-2, Prior IL-2

IL-15

IL-7