T Cell Immunotherapy - Optimizing Trial Design

Session I
Current Status of Cancer Immunotherapy: Trials, Results, and Challenges

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# Overview of Trials

<table>
<thead>
<tr>
<th>Protocol number/title</th>
<th>#1655: Phase I/II Study of Adoptive Immunotherapy with CD8+ WT1-specific CTL Clones for Patients with Advanced AML, ALL, MDS, or CML after Allogeneic Hematopoietic Stem Cell Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease indication/Research Participant population</td>
<td><em>High-risk Leukemias post HCT:</em> MDS RAEB or RAEB-T, CML beyond chronic phase, AML beyond first remission, Ph⁺ (<em>BCR-abl</em>) ALL at any stage, any ALL beyond 1st remission, primary refractory AML or ALL, and secondary AML.</td>
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<tr>
<td>TCR or CAR product (ex vivo cell/vector/transgene) and Dose</td>
<td>HLA A*0201 restricted, donor-derived WT1-specific (RMFPNAPYL) CD8⁺ clones. Escalating doses of WT1-specific CTL of 3.3x10⁸, 1.0x10⁹, 3.3x10⁹, and 1 x 10¹⁰ CTL/m² with the last cell dose followed by low-dose s.c. IL-2 (250,000 IU/m² twice daily) x 14 days.</td>
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</tbody>
</table>
| Trial initiation date/status/enrollment | From 03/2006 to 08/2010, 37 patient/donor pairs were enrolled  
  • 11 patients received CTL infusions  
  • 3 patients alive at 42, 40 and 30 months after CTL infusion, and 47, 45 and 50 months after HCT respectively  
  • Trial is closed to accrual. |
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<th>Protocol number/title</th>
<th>#2498: Phase I/II study of adoptive immunotherapy with virus specific CD8+ T cells transduced to express a WT1-specific TCR for patients with high risk or relapsed AML, MDS, or CML</th>
</tr>
</thead>
</table>
| **Disease indication/Research Participant population** | **High-risk Leukemias post HCT:** AML beyond 1\textsuperscript{st} remission and secondary AML, MDS RAEB or RAEB-T, CML beyond chronic phase, .  
• Arm 1/prophylaxis: no evidence of disease post-HCT.  
• Arm 2/treatment: refractory/relapsed disease post HCT. |
| **TCR or CAR product (ex vivo cell/vector/transgene) and Dose** | Virus (EBV/CMV)-specific CD8\(^+\) T cells transduced to express a characterized HLA A*0201-restricted WT1-specific TCR (TCR\(_{c4}\)).  
• Escalating doses of CTL\(_{c4}\) of 1.0x10\(^9\), 3.3x10\(^9\), 1 x 10\(^{10}\) and 1 x 10\(^{10}\) CTL/m\(^2\) followed by low-dose s.c. IL-2 (250,000 IU/m\(^2\) twice daily) x 14 days (Arm 1: q4 weeks, Arms 2: q2 weeks). |
| **Trial initiation date/status/enrollment** | Trial is open to accrual and actively enrolling since 03/2013.  
• 10 patients are currently enrolled  
• 2 completed treatment on Arm 2 (3\textsuperscript{rd} patient received only 3 of 4 planned infusions due to progression)  
• 1 completed treatment on Arm 1.  
• 2 additional patients scheduled to receive CTL\(_{c4}\) in the next month |
Lessons Learned

• Protocol 1655:
  – Targeting WT1 does not appear toxic to tissues expressing physiological levels of WT1 (kidney, lung)
  – No new-onset GVHD observed within 3 months of CTL infusions
  – Anti-leukemic activity was observed in a subset of patients, and correlated with detection of CTL clones in vivo.
  – Long-term persistence of CTL clones in vivo was observed in the subset of patients who both received clones primed with IL-21 and had no detectable leukemia/MRD at time of infusion
  – The avidities of the clones obtained were variable (50% target lysis ranging over 4 logs, from $10^{-1}$ to $<10^{-4}$ ng/ml).
  – More reproducible clinical results might be achieved if the infused CTL exhibited more consistent comparably high avidities and persisted in vivo.
Lessons Learned

- **Protocol 2498:**
  - Targeting WT1 with a characterized, **higher affinity TCR** (50% target lysis $\sim10^{-4}$ ng/ml) was **not toxic** at doses $\leq 10^{10}$ cells/m$^2$ to tissues expressing physiological levels of WT1 (kidney, bone marrow) in the 3 patients treated to date.
  - **Persistence** ($>0.05\%$ multimer$^+$ CD8$^+$ cells) observed in all treated patients **up to 28 days** after last infusion (range 0.051%-10.6%).
    - Maximum frequencies at 1-3 days infusions (range 1.42%-30.4%)
  - Efficacy (inconclusive/data too preliminary).
    - 2 patients on Arm 2: 1 had a chloroma and progressed and one had MRD detected by flow (0.03%) that decreased to 0.006% after 4 infusions
    - One patient on Arm 1 (prophylactic: no detectable disease)
• **Protocols 1655 and 2498**: No serious or unexpected toxicities

• **Toxicities observed (most common):**
  – Lymphopenia (transient)
  – Fever/chills within 24 hours of infusions compatible with a cytokine release syndrome. Spontaneous resolution observed in all cases.
  – Injection site reactions due to low-dose s.c IL-2.