Dosing Strategies: Goals and Options

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Dosing Strategies: Goals and Options

• Starting doses: Is there a usual range?
• Single versus Split: Rationale and improved safety
• Dose escalation: Single subject versus 3 subject cohorts?
Dosing T cells: Treatment Doses

- **NCI (CD19-28z CAR)**
  - Low grade B cell malignancies: $3 \times 10^6 - 3 \times 10^7$ CAR T cells/kg (single infusion, dose escalation)
- **UPenn (CD19-4-1BBz CAR)**
  - CLL: $1.45 \times 10^5 - 1.6 \times 10^7$ CAR T cells/kg (split infusion, no dose escalation)
    - Kalos et al STM 2011
  - ALL: $1.4 \times 10^6$ and $1.2 \times 10^7$ CAR T cells/kg (split infusion, no dose escalation)
    - Grupp et al NEJM 2013
- **MSKCC (CD19-28z CAR)**
  - CLL: $4 \times 10^6 - 3 \times 10^7$ CAR T cells/kg (split infusion, dose de-escalation)
    - Brentjens et al Blood 2011
  - ALL: $1.5 - 3 \times 10^6$ CAR T cells/kg (split infusion, aborted dose escalation)
    - Brentjens et al STM 2013
- **BCM (CD19z and CD19-28z CAR)**
  - B cell lymphoma: $2 \times 10^7 - 2 \times 10^8$ CAR T cells/m² (multiple infusion, dose escalation)
    - Savaldo et al JCI 2011
- **FHCR (CD20-28-4-1BBz CAR)**
  - Low grade B cell lymphomas: $4.4 \times 10^9$ CAR T cells/m² (multiple infusion)
    - Till et al Blood 2012
Treatment Doses: Conclusions

- Generally all total treatment doses fall within a similar range of roughly $3 \times 10^6$ - $3 \times 10^7$ CAR T cells/kg in currently published clinical trial results.
- Outlier(s) with very low T cell infusion numbers have been reported ($1.45 \times 10^5$ CAR T cells/kg).
- There does not appear to be a correlation at this time based on the published literature between dose and clinical outcome.
- Multiple variables need to be considered: disease treated, CAR design, conditioning chemotherapy, and gene transfer technology.
- It remains possible that under optimal conditions, optimal T cell generation protocols, optimal phenotype of infused CAR T cells, equally effective clinical outcomes may be achieved with significantly lower T cell doses.
- Lower T cell dosing, with equal efficacy may markedly alter the fiscal feasibility of this technology moving forward.
- To date there is no reliable data to suggest a correlation between T cell dose and observed toxicity.
## Table 1  Cyclophosphamide and T-cell doses in IRB protocol no. 06-138

<table>
<thead>
<tr>
<th>Step</th>
<th>Cyclophosphamide</th>
<th>CAR + T-cell dose</th>
<th>No. of enrolled subjects</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0 g/m²</td>
<td>$1.2-3.0 \times 10^7$/kg</td>
<td>3</td>
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<tr>
<td>3</td>
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<td>$0.4-1.0 \times 10^8$/kg</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>1.5 g/m²</td>
<td>$4.0-10 \times 10^6$/kg</td>
<td>2</td>
</tr>
</tbody>
</table>

CAR, chimeric antigen receptor; MTD, maximum-tolerated dose.
Single versus Split Dosing: Rationale

(a) Temperature (°C)

(b) Creatinine, Phosphorus, Potassium, Uric acid
Cytokine Profiles of IRB # 06-138 patient 4 during therapy

Figure 2  Serum cytokine concentrations measured in subject 4. Serum samples were obtained 30 days before cyclophosphamide (−30 d), 2 hours before T-cell infusion (−2 h), and 4 and 26 hours after T-cell infusion (+4 h, +26 h, respectively). The −2-h sample is therefore post-cyclophosphamide but pre-T-cell infusion. Pretreatment tumor necrosis factor-α (TNF-α) serum values were 200, 50, and 59 ng/ml in subjects 1, 2, and 3, respectively. IFN-γ, interferon-γ; IL, interleukin.

Brentjens et al Mol Ther 2010
Split dosing: Rationale (?)

- Toxicity of Patient 4 treated on protocol 06-138 prompted amended clinical trial design to enhance safety of CAR T cell infusions with split dose infusions.
- Detailed cytokine analyses of toxicity in this patient suggests prior infectious process as the source of toxicity.
- To enhance safety, despite the fact that there is NO data to suggest CAR T cell toxicity in this setting, we proposed to split dose infusion of CAR T cells to enhance the safety of this therapy.
- To date all data presented on this death on study is related to a prior sub-acute infectious process with NO data to suggest that this outcome was related to infusion of CD19-targeted CAR T cells.
Schema of NCI Clinical Trials

Figure 1. Anti-CD19-CAR–transduced T-cell production and clinical treatment protocols. (A) PBMCs were stimulated with the anti-CD3 mAb OKT3 on day 0. The cells were transduced with gammaretroviruses encoding the anti-CD19 CAR on days 2 and 3. On day 10, a rapid expansion protocol was started, and the cells were ready for infusion on day 24. (B) Patients received 60 mg/kg cyclophosphamide chemotherapy daily for 2 days. Next, patients received 25 mg/m² fludarabine chemotherapy daily for 5 days. One day later, the patients received a single infusion of anti-CD19-CAR–transduced T cells. Starting on the same day as the T-cell infusion, the patients received IV IL-2 every 8 hours.
UPenn CD19 CART T cell therapy of CLL

Kalos et al Sci Tran Med 2011
Split Dosing: Other Centers

• MSKCC
  – Split dosing days 2 and 3 post conditioning chemotherapy (33% then 67% of T cell dose)

• BCM
  – Single infusion, second infusion possible with SD or disease response

• FHCRC
  – Split dose infusion (2-5 days apart, with dose escalation)
Conclusions regarding T cell split infusion protocol

• There is no data, to date, to support enhanced safety with split dose T cell infusions.
• Safety concerns which prompted split dose T cell infusions upon refection do not appear to be based on toxicities associated with CAR T cell infusions (MSKCC experience).
• Overall, multiple dosing needs to be considered in the context of disease response versus toxicities associated with a single T cell infusion.
Dose escalation: Single subject versus 3 subject cohorts?

- None of the cited protocols include dose escalation of T cells dose within a single patient.
- Most protocols to date, with limited numbers of published patient outcomes, lend very little data with regard to dose escalation making subjective conclusions regarding any dose escalation (single subject versus 3 subject cohorts) difficult to evaluate at this time.
An additional but more relevant question to address: Multiple CAR T cell infusions

- Several current protocols stipulate additional CAR T cell infusions after the initial treatment (UPenn and BCM)
- At MSKCC, we are investigating additional T cell infusions in ALL patients ineligible for Allo-BMT or those who have relapsed after initial CAR T cell therapy
- It remains to be seen what if any role additional “consolidation” CAR T cell infusions may have in the setting of relapsed disease, transplant ineligible patients, or in the setting of limited CAR T cell persistence.