Case report of a Serious Adverse Event upon administration of T cells transduced with a MART-1 specific T cell receptor

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Disclosure slide

• No conflict of interest
Clinical ACT program NKI-AVL

• TIL treatment melanoma
  – Current status: 7 patients treated in phase I/II feasibility trial
  – Future: Randomized multicenter phase III trial
    • TIL treatment vs ipilimumab as first line treatment (n=162)
    • In collaboration with:
      – Herlev Hospital, Copenhagen (Inge Marie Svane & Marco Donia)
      – University of Manchester (Robert Hawkins & Ryan Guest)

• MART-1 TCR transduced T cells
Trial design

Design $1D3_{\text{opt}}$ HMCys TCR construct:

- $1D3$ TCR recognizes MART-I 26-35 epitope (not affinity-matured)
- MP71 retroviral vector
  

Expansion IL-7/IL-15 + aCD3/aCD28 beads

- “Less differentiated” phenotype compared with IL-2 + aCD3 mAb
- Better engraftment in humanized mouse model
  
Trial design

Patient group: Stage IIIc/IV melanoma

Clinical protocol:

- Non-myeloablative chemotherapy
cyclophosphamide/fludarabine

- T cell infusion

- Low-dose interleukin-2
  (2x10^6 IU/once daily up to two weeks)
Patient 1

• 43 year old female
• Bulky disease with two large abdominal metastases (16 and 18 cm)
• Multiple pulmonary, subcutaneous and lymph node metastases of 1-3 cm
• One small brain metastasis of 8mm
• Large volume (~10L) ascites
Infusion product: characteristics

- Transduction efficiency 61%
- $4.56 \times 10^9$ transduced cells
- CD8$^+$/CD4$^+$ ratio 80/20
- Sterile
- Functional *in vitro*
Clinical course

- T cell infusion at day 0
- At day 1, patient developed high fever (>40°C)
- Blood positive for ESBL at day 1
- Patient treated with imipenem and vancomycin
- Stabilized during following days, no signs of sepsis
- Vancomycin discontinued at day 4
- Patient showed fluid retention
- No sign of on-target toxicity against MART-1
Clinical course

- Morning of day 6, not responding to verbal stimuli
- Fever of 39.5°C, high pulse (110/min)
- Antibiotic regimen changed to meropenem, vancomycin and amoxicillin
- Transport to ICU. Generalized tonal clonal convulsion.
- Cardiac arrest
- Intubated and resuscitated for 10 minutes
- Kept in coma
- CT scan showed brain edema and bleeding of lesion
- All cultures remained sterile (sputum, BAL, ascites, liquor)
- No meningitis
- No tumor lysis syndrome
- After 48 hours, sedation stopped, no neurological improvement → patient died on day 9 from multiple organ failure
Possible explanations

1. Bacterial sepsis
2. Cardiac arrhythmia or asphyxia induced by convulsion
3. T cell related
   a) Recognition other MHC-peptide complex
   b) Cytokine release
Post mortem examination

- Lymphocytic myocarditis with influx of CD3/CD8/GranzymeB/MART-1 TCR^+ cells
- Extensive infiltration of CD3/CD8/GranzymeB/MART-1 TCR^+ cells in peritoneal metastases
- Minor T cell infiltration in other organs
  - Brain: 2 cerebral metastases and a 2 cm hemorrhage (CVA) in
Clinical chemistry

Increased:  S100B
            Procalcitonin
            NT-proBNP
Immunological assays

- TCR modified T cells could be detected on day 7

**Graphs showing percentages of CD8+ cells in PBMCs, BAL, and Ascites with MART-1 tetramer staining.**
Immunological assays

- Consecutive rise of IFN-γ and IL-6

- Same profile BAL and ascites
Possible explanations

1. Bacterial sepsis
   Pro: High CRP, procalcitonin and IL-6
   Con: Cultures blood, ascites, BAL and liquor after ICU negative. ESBL infection under control

2. Cardiac arrhythmia or asphyxia induced by convulsion
   Pro: Thrombocytopenia by myeloablative chemotherapy could result in hemorrhage, followed by convulsions
Possible explanations

3. T cell related
   a) Recognition other MHC-peptide complex
      – Unlikely HLA-A2-restricted epitope
      – No reactivity against HLA-A2\(^+\) beating cardiomyocyte culture (Immunocore)
      – Alloreactivity against cell lines expressing a panel of common HLA alleles was absent
      – Reactivity against allogeneic HLA molecule in complex with a (heart) tissue specific antigen possible
      – No evidence in favour, infiltrated cells in myocard can be induced by infection, heart failure and/or resuscitation. No abnormalities
Possible explanations

3. T cell related
   b) Cytokine release
      - Strong peak in IFN-γ shortly after T cell infusion
      - Increasing concentration of serum IL-6 towards toxic levels
      - Increased IL-6 levels previously observed in CD19 CAR trials
      - Co-incubation T cell product with tumor cell line results in IL-6 production

(Porter et al. NEJM 365(8): 725-33, 2011)
Cause unexpected death

- Cannot fully be explained
- Possibly multiple factors
- Thrombocytopenia $\rightarrow$ hemorrhage $\rightarrow$ convulsion $\rightarrow$ heart problems
- High levels of cytokines possibly a major component
Adjustments M11TCR protocol

• More strict patient inclusion
  – No bulky disease/ascites
  – No brain metastases
• Full cardiac evaluation
• Lower cell number in next patients
  – 1st cohort: $5 \times 10^7$ transduced cells
  – 2nd cohort: $5 \times 10^8$ transduced cells
  – 3rd cohort: $5 \times 10^9$ transduced cells
• Clinical monitoring IL-6 levels
  – Infusion of anti-IL6R Ab (tocilizumab)
• Infusion of corticosteroids and anti CD52 Ab in case of severe toxicity
• Second patient received cells last Monday
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