The challenges of conducting trials of Advanced Therapies

The CAR trials

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International Clinical Trials Day – 20th May 2016
The Cancer Research UK & UCL Cancer Trials Centre

**Expertise in:**
- Brain Cancer
- Gastrointestinal cancer
- Gynaecological cancer
- Head & neck cancer
- Leukaemia
- Lung cancer
- Lymphomas & myeloma
- Metastatic cancer – Radiation studies
- Sarcoma
- Advanced Therapies
- Regulatory Group
- Statistics Group
- IT and Database Unit
- Training

**Formed in 1997**

**One of the largest Cancer Trials Centres in UK**

**Full UKCRC registration**

**Advanced Therapy Trials at the CTC**

**Active:**
- ICAT
- CARPALL
- COBALT
- TRIOC

**In set-up:**
- CARD
- ITREC
- TACTICAL

**In follow-up:**
- CD19TPALL

**Planned CAR trials:**
- Relapsed primary CNS lymphoma
- Acute Lymphoblastic leukaemia

[www.ctc.ucl.ac.uk](http://www.ctc.ucl.ac.uk)
What are Advanced Therapies?

Biological medicinal products

- **Gene Therapy**
  - To regulate, repair, replace, delete or add a genetic sequence

- **Cell Therapy**
  - To treat, prevent or diagnose a disease

- **Tissue Engineered Product**
  - To regenerate, repair or replace a human tissue

**Combined ATMP: Medical Device + cells/tissue**

[EC Regulation No 1934/2007]
Chimeric Antigen Receptors – CAR

...are artificial T cell receptors

T cells are genetically engineered to produce special chimeric antigen receptors on their surface. CARs are proteins (antibody) that allow T cells to recognize a specific protein (antigen) on cancer cells.

V. Brower, New Scientist: April 1, 2015

(CAR-) specific antibody targeting CD19 antigen on B-cell malignant cells
Strict lineage restriction makes CD19 an ideal target
Why do we do these trials?

Rational
• Patient population with poor prognosis
• Recent advances with CAR-redirected T cell therapies

Objectives
• Feasibility, safety, toxicity
• Cell engraftment, expansion and persistence of CAR T cells in patients
The challenges of Advanced Therapy trials

- Additional regulatory & GCP requirements
- Product traceability and record retention
- Manufacturing capacity
- Site facilities & logistical considerations
- Safety management and reporting
- Dose escalation decisions
What are the main risks of CD19-CARs?

- First in human or early phase
- Possibly serious/life threatening immune-mediated side effects

**Cytokine release syndrome**
Fever, fatigue, hypotension/tachycardia
nausea, capillary leak, multi organ system failure

**“On target, off-tumour” toxicity**

**Neurological toxicity**
Confusion, delirium, aphasia, seizure
Risk Mitigation

Early toxicity:
• Clinical risk management plan
• Staggered recruitment and treatment
• Patient monitoring
• Co-expression of suicide gene

Late toxicity:
• Immunoglobulin transfer
In summary...

- High risk trials
- Small but logistically complex
- Additional regulatory requirements

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