Safety Issues with CAR T cells – Lessons Learnt

CIRM Webinar: CAR-T Cell Immunotherapy: Challenges and Opportunities Using Mature or Stem Memory T Cells

March 18, 2015

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Outline

- Types of Adverse Events (AE's)
  - Acute Infusion reactions
  - On-target toxicities
    - Tumor Lysis Syndromes
    - Cytokine Release Syndromes (CRS)
    - Organ-specific toxicities
- Trial design considerations to minimize risks
  - Eligibility
  - Treatment Plan
  - Dose-escalation schemes
  - Defining Dose Limiting Toxicities
  - Re-treatment
  - Ancillary evaluations
  - Risk mitigation
  - Long-term Follow Up

CAR T cells - Acute Infusion Reactions

Clinical manifestations:

- Immediate
- Fever
- Chills
- Hypotension
- Bronchospasm

CAR T cells - Acute Infusion Reactions

Possible causes:

– DMSO

– Cell mediated

CAR T cells - On-target Toxicities

- Tumor Lysis Syndrome
- Cytokine Release Syndrome (CRS)
- Organ specific toxicities

CAR T cell toxicity – Tumor Lysis Syndrome

Tumor Lysis Syndrome

- Urinary symptoms
- Renal failure from elevated uric acid levels
- Abdominal pain
- Electrolyte abnormalities
  - Hyperkalemia – weakness, cardiac rhythm abnormalities
  - Hypocalcemia – cramps, tetany, cardiac rhythm abnormalities

CAR T cells toxicity - CRS

- Clinical Manifestations
  - Life-threatening
  - Hypotension
  - Fever
  - Hypoxia
  - Multi-organ failure
  - Coagulation disorders

CAR T cells toxicity – CRS

- Pathophysiology
  - Elevated cytokine levels
    - IL-6, IFN-gamma, TNF-alpha are currently thought to be the key mediators of CRS.
    - Role of other elevated cytokines in CRS and organ toxicity is currently being evaluated.

CAR T cells – Organ-specific toxicities

- Off-tumor Toxicities
  - Vital Organs
    - CNS
      - CNS depression with lethargy requiring intubation for airway protection – CAR T CD-19 -specific products
      - Seizures
      - Cognitive abnormalities
    - Pulmonary
      - Immediate death with congestion of the lungs with activated T cells
  - Non-vital Organs
    - Hepatic
      - Abnormal liver enzyme elevation with CAR T cells targeting Carbonic anhydrase-IX

CAR T cells - Long-term Risks

- Insertional Mutagenesis
- B-cell aplasia (with B-cell targeted products)

CAR T cells –Safety Considerations in Designing Trials

- Eligibility
- Treatment Plan
  - Starting dose
  - Conditioning regimen
  - Risk mitigation plans
- Dose-escalation schemes
- Defining Dose-Limiting Toxicities
- Re-treatment
- Ancillary evaluations
- Risk mitigation
- Long-term Follow-Up

CAR T cell trial design – Eligibility

- Including multiple histological tumor types that express the same tumor antigen
- Logical sense to combine and streamline clinical development
  - –Issues to consider
    - •Early-phase trials –
      - –Disease-related co-morbidities
      - –Sample size to detect early efficacy signals
      - –Toxicity profile may vary depending on histology
      - –Similar clinical activity

CAR T cells – Safety issues from CAR Generation perspective

- First generation CARs
  - Single - chain variable fragment (scFv) linked to the transmembrane and intracellular signaling domains of either CD3ζ or FcRγ
  - Limited activation, anergy and poor expansion
  - Toxicity profile was more favorable.
- Second generation/Third generation CARs
  - Addition of intracellular domain of the co-stimulatory molecules
  - Increase activation and expansion
  - Wider spectrum of toxicities

CAR T cell trial design - Starting doses

Challenges to selection

– Paucity of animal models

– First in Human product – limited “a priori” information

– *In-vivo* expansion of cells is unpredictable

– Limitations to “borrowing” safety data from first generation CAR T product

Current Approach

– Extrapolate the safety data from related products (TILs, “similar” TCR re-directed cells, “similar” class of CAR T product,) less than optimal

– Extrapolate the safety data using the same product in histologically different tumor type(s)

CAR T cells trial design – Conditioning regimen

Issues:

- Associated with toxicities
- Toxicities differ based on the regimen
- May overlap with CAR T toxicities
- Optimal regimen and role in CAR T treatments are evolving

Recommendations:

- Narrow the choice of regimen
- Explore the activity and safety profile of the CAR T cells +/- conditioning regimen

CAR T cells toxicity – Risk mitigation

- Defining triggers for medical intervention
  - Grading CRS based on need to intervene
  - Biomarkers that predict severity of CRS
- Identifying medications
  - Steroids
  - IL-6 receptor blockade
  - TNF blocker
- Treatment algorithms
  - Dosing frequency
  - Sequencing use of the medications
- “Suicide” genes

CAR T cell trial design: Dose escalation schemes

Accelerated titration design

- Correlation between dose and toxicity not known
- Class of product has substantial toxicities
- *In-vivo* activity varies
- Product differences (antigen-specific binding domains differ, vector's differ) – limit leveraging cross-study safety data

CAR T cells trial design: Dose escalation schemes

Current recommendation

– Accelerated titration design sub-optimal

– 3+3 design is more common

Personalized product

- *in-vivo* activity differences
- Differences in tumor antigen burden
- Product characterization differences

– CRM model applicable but in limited situations

CAR T cell trial design: Dose Limiting Toxicity

- Defining Dose Limiting Toxicity (DLT)
  - Reasonable to consider exceptions
  - Expected toxicities should not necessarily mean that they should be excepted from DLT definition
    - Severe expected toxicities
    - Prolonged vital organ toxicities
- Contingency plans
  - Dose de-escalation
  - Revised DLT criteria (on a case-by-case basis)

CAR T cell trial design – CRS Grading

- Traditionally based on CTCAE criteria
- Other grading criteria have been proposed
- Advantages to a single grading criteria in understanding cross IND safety issues
- Important role in implementing risk-mitigation treatments

CAR T cells trial design: Reporting toxicities

Dose and Toxicity Assessment Approach

- Helpful to have safety reports that include total dose, total transduced cell dose, transduced cell dose/kg and/or BSA
- May need to assess toxicity in the context of histology
- May need to consider the extent of tumor burden into the dose-toxicity relationship
- Impact of split dose vs single dose administration
- Impact of conditioning regimens

CAR T cell trial design: Re-treatment

Challenges:

– Paucity of pre-clinical data

– Unknown safety profile in humans

– *In-vivo* persistence

– Interval between doses

– Clinical activity during the initial cycle

– Intra-patient dose escalations

CAR T cell trial design: Re-treatment

Considerations when planning re-treatment

– Safety criteria
  - Dose
  - Organ function
  - Performance status
  - Adverse events experienced during prior treatment
  - Persistence and expansion of the CAR T cells

–Clinical activity criteria
  - Partial remission (PR)
  - Progressive disease (PD)
  - Complete remission (CR) with minimal residual disease (MRD)

CAR T cell trial design: Ancillary Evaluations

In-vivo Cytokine Profile

– Range of cytokines evaluated

– Frequency of monitoring

– Assays

– Comparative data between subjects who do and do not experience CRS

– Correlative data between cytokine levels

– Real-time vs batched assessments

– Reporting to the FDA

CAR T cell design: Risk Mitigation Strategies

Pre-specify plans

- Medications
  - Types
- Treatment algorithm
  - Triggers for medical intervention
  - Sequencing drugs
  - Activating suicide genes
  - Cytokine data collection

CAR T cell design: Reporting

- Reporting and data analysis
  - Timing of reporting
  - Streamlined format for collecting and reporting
- Benefits
  - Improves understanding of safety issues
    - Within an IND
    - Across-INDs
  - Provides consistent advice
  - Supports clinical development

Summary

- CAR T cells are novel products that have unique characteristics that may impact clinical aspects of regulating these products.
- There are challenges with almost every aspect of the trial design, from eligibility to long-term follow-up.
- Safety analysis of CAR T product is complex as it takes into consideration manufacturing aspects of the product in conjunction with clinical data.
- A uniform approach to grading, assessing and reporting toxicities improves our understanding of the safety of these products.
- Evaluating toxicities from a regulatory perspective requires frequent interactions with sponsors.
- CAR T cell science is a moving target and maintaining regulatory flexibility as knowledge improves is key to supporting drug development.

Acknowledgments

OCTGT T Cell Working Group

- Kristin Baird, MD
- Andrew Byrnes, PhD
- Robert Le, MD, PhD
- Ke Liu, MD, PhD
- Jinhua Lu, PhD
- Brian Niland, PhD
- Maura O'Leary, MD
- Graeme Price, PhD
- Mercedes Serabian, MS
- Daniel Takefman, PhD
- Ramjay Vatsan, PhD
- Allen Wensky, PhD
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