Safety Issues with CAR T cells – Lessons Learnt

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