NATIONAL CANCER INSTITUTE
Center for Cancer Research

CAR T-cells—Beyond the Storm:
Long Term Toxicities, Hypogammaglobulinemia, Cytopenias and Infection Risks

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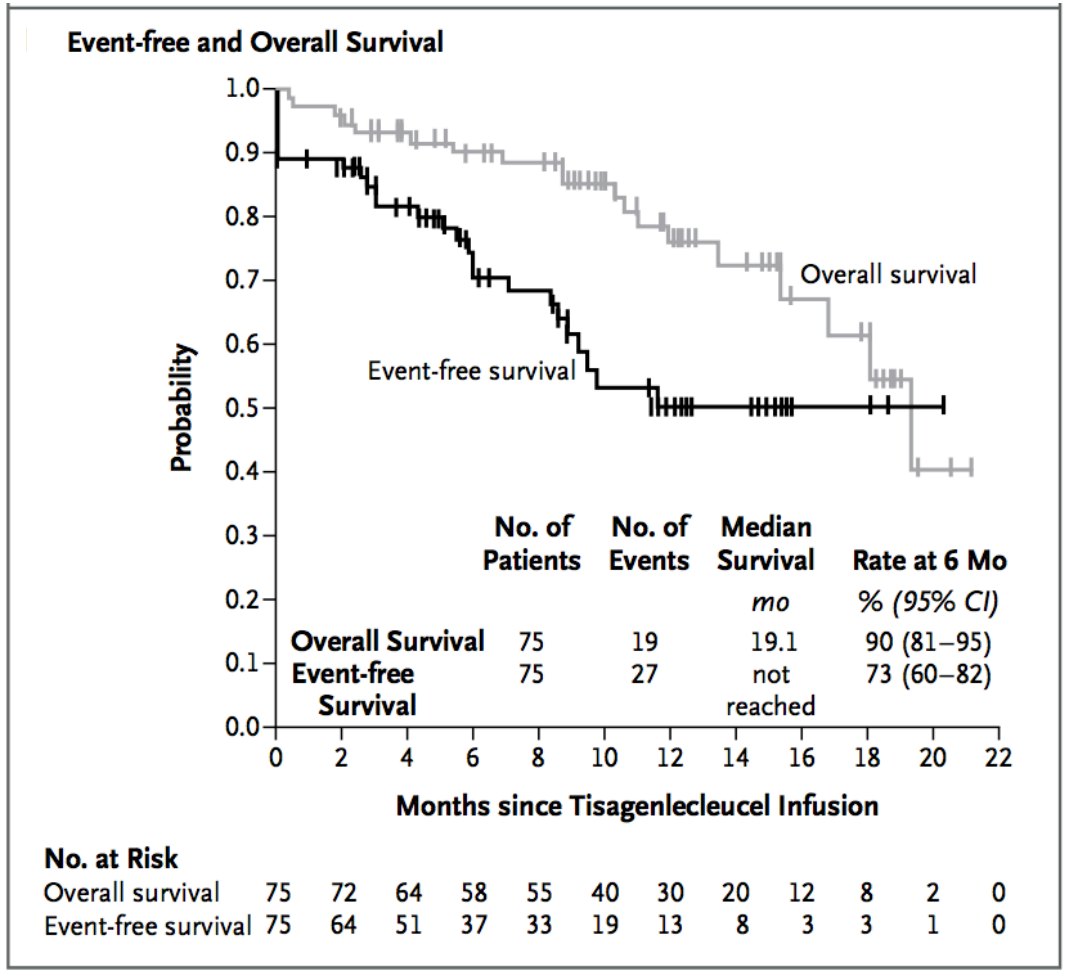
Disclosures

- None

CD19 CAR T-cells may be curative in select patients with B-cell malignancies

CAR T-cells highly effective in pediatric B-ALL and adult NHL

- CD19 CAR T-cells
- 4 constructs FDA approved
  - 1 for children/young adults with B-ALL
- Current efforts focused on understanding the limitations for durable remission and optimizing long-term outcomes



Maude SL, et al. NEJM 2018

What are the implications of using CAR T-cells for long-term cure?

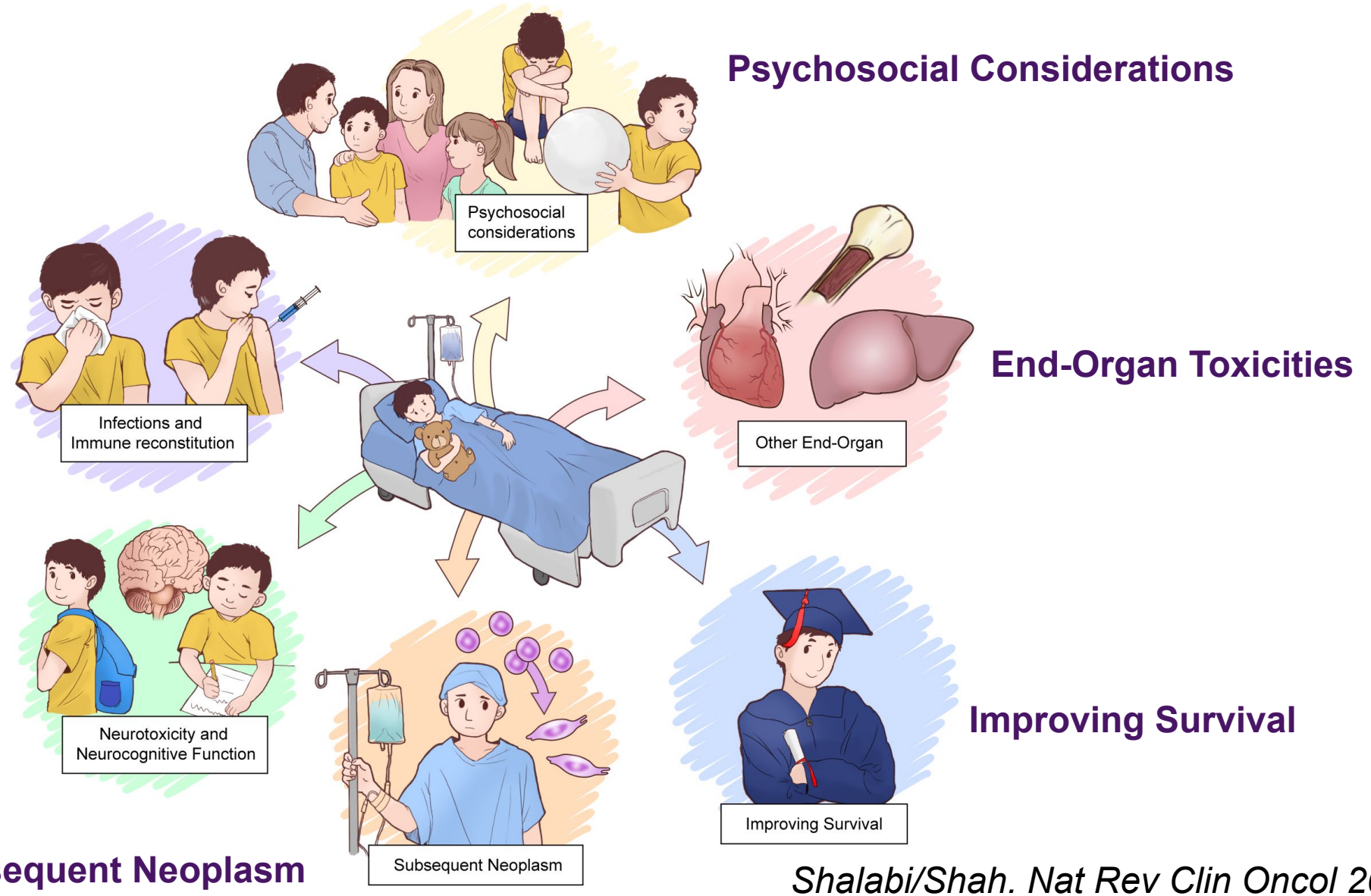
Benefits

- Spare additional therapies
  - Alterative options: +/- more intensive or ineffective
- Prolong survival
- Patient population:
  - Heavily pre-treated
  - +/- prior transplant
  - Need for alternative approaches

Toxicities

- CAR Toxicities: Vast experience in **acute** toxicities
  - Cytokine release syndrome (CRS)
  - Neurotoxicity (ICANS)
- **Limited experience in sub-acute or longer term toxicities**

Critical Areas of Ongoing Investigation



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Neurotoxicity and Neurocognitive Function

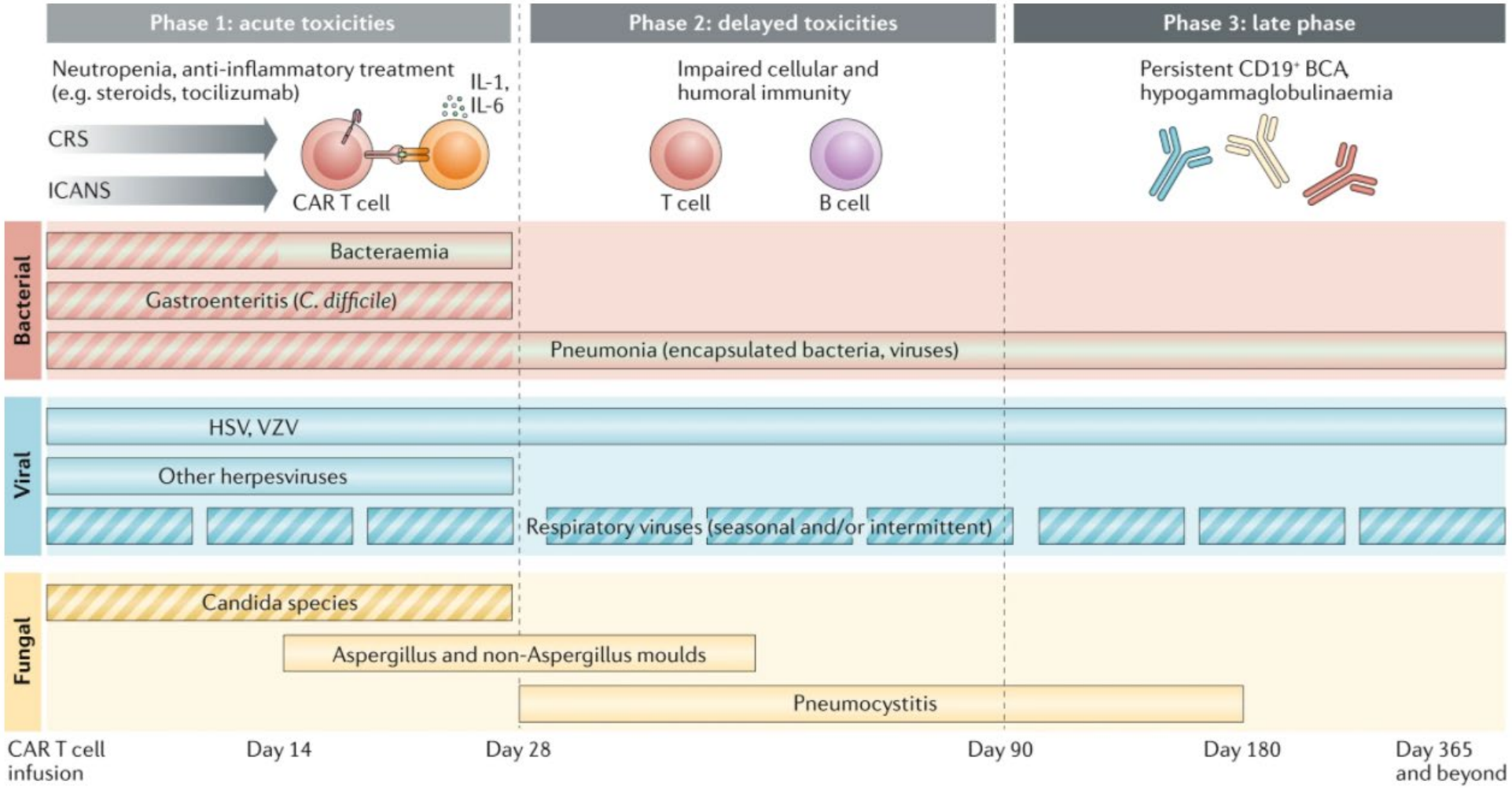
Impact of Prior Therapy

- Intrathecal chemotherapy
  - Methotrexate
- CNS leukemia involvement
- CNS radiation
- Age at treatment
  - Neurocognitive function

Following CAR T-cells

- Neurotoxicity (acute) appears to be largely reversible
  - ? Late or chronic effects?
  - Impact based on severity of neurotoxicity
- What neurotoxicity is spared?
- How does neuroimaging change over time?
- Implications for CNS tumor directed CAR T-cells

Infectious Complications



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***Josh Hill, U of Washington*

Bone Marrow Toxicities

- **Symptoms**:
  - Prolonged cytopenias and persistent marrow dysfunction
  - Autoimmune cytopenias?
- **Etiologies**:
  - Leukemia
  - Prior chemotherapy/HSCT
  - Cytokine mediated
  - HLH/MAS
- **When to consider intervention?**
  - What is the impact?
  - Duration?
  - Transfusion dependence?
- **Interventions**:
  - Growth factor support?
  - CD34+ stem cell boosts
  - Allogeneic HSCT
  - Need for guidelines

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***Timothy Olson, CHOP*

Immune Reconstitution and Hypogammaglobulinemia

- B-cell aplasia is an expected (? and desired) outcome
- Immunoglobulin replacement
  - Guidelines vary (children versus adults, IV versus SQ, and what threshold to give)
  - Implications/cost
- Infectious complications
  - Particularly with concurrent cytopenias
- Vaccination:
  - When and what will the response be?

Strategies to prevent infections after CAR T-cell therapy

Types of immune dysfunction	Causes	Infectious complications	Mitigation strategies	Active research topics
Neutropenia	Underlying disease Lymphodepleting chemotherapy Prolonged cytopenia after CAR T cell treatment	Bacterial infections Fungal infections	Prophylaxis for bacterial and fungal infections until neutropenia resolves Consider filgrastim	Define best practice for prophylaxis in this patient population Aetiology of prolonged cytopenia Correlation between CRS and infections
Lymphopenia	Prior chemotherapy Underlying disease Lymphodepleting chemotherapy	Viral reactivation (for example, of VZV) Viral and fungal infection (for example, resulting in PJP)	Viral prophylaxis Prophylaxis against PJP	Determination of duration of prophylaxis Correlation between BCA and $CD4^+$ T cell counts
Hypogammaglobulinaemia	BCA	Sinopulmonary infections	Immunoglobulin replacement with IVIG or subcutaneous immunoglobulin	Define extent of humoral immunity preservation in patients with ongoing BCA Define optimal immunoglobulin replacement strategy, including duration of administration Determine efficacy and utility of vaccination in the setting of ongoing BCA

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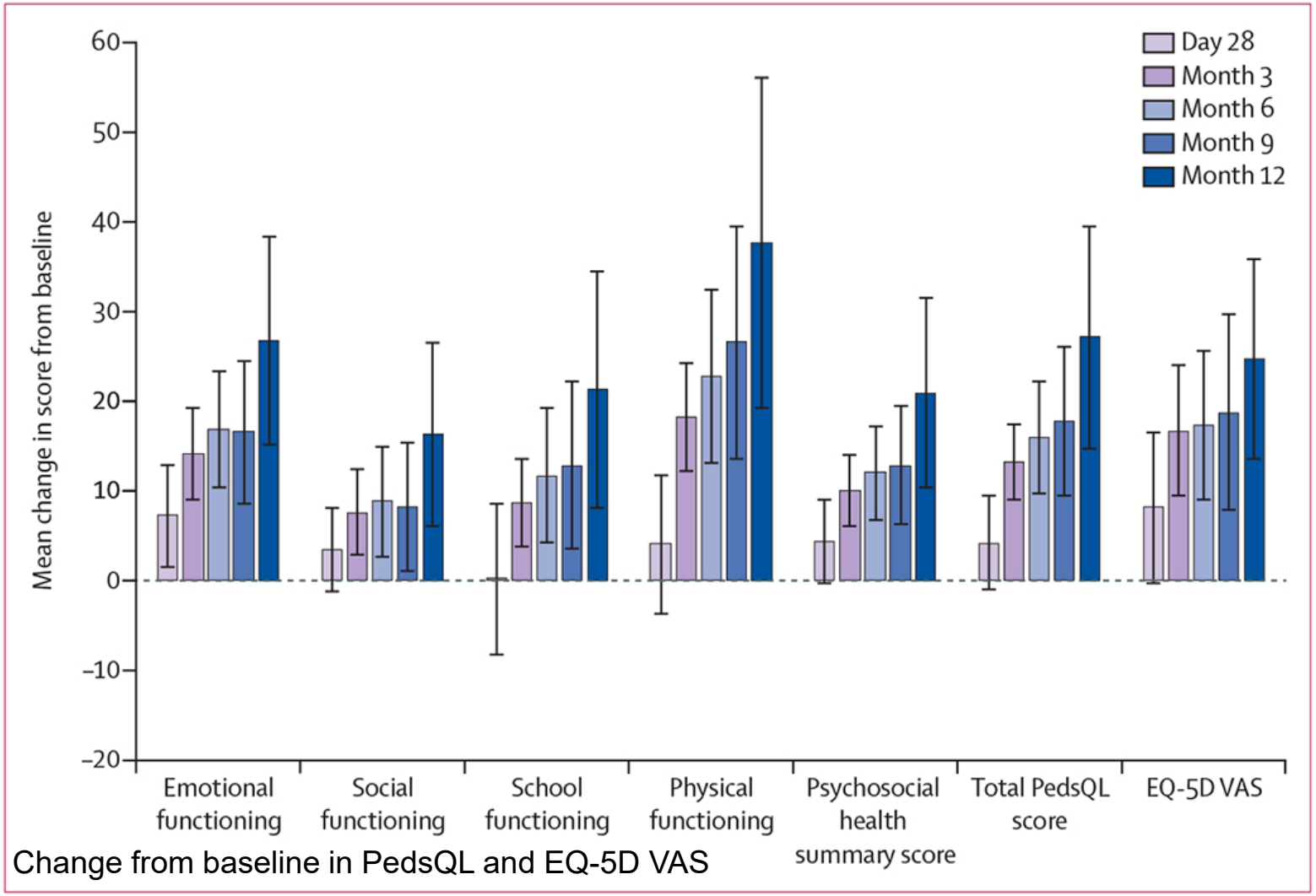
Other end-organ toxicity considerations

Organ system	Toxicity	Proposed surveillance studies
Bone marrow	Haemophagocytic lymphohistiocytosis Cytopenias, including grade 3–4 neutropenia and thrombocytopenia	Baseline CBC/D and bone marrow prior to lymphodepletion Frequent laboratory assessments including CBC/D, hepatic panel, inflammatory markers (such as C-reactive protein and ferritin), bone marrow aspirate or biopsy to evaluate cellularity and assess for haemophagocytosis, dysplasia or relapse
Cardiac	Sinus tachycardia Hypotension Shock requiring inotropic support Depressed systolic ejection fraction Cardiac arrhythmias Cardiac failure or arrest	Baseline electrocardiography, transthoracic echocardiography, biomarkers[a] Cardiology consultation[b] Consider cardiac monitoring, repeat transthoracic echocardiography and biomarker assessments[a] in patients with CRS grade ≥2 Follow-up electrocardiography, transthoracic echocardiography, and biomarkers[a] 1 month after infusion, with serial evaluations in patients who develop cardiac dysfunction or in those with persistent symptoms
Pulmonary	Hypoxia Cough Pulmonary oedema Acute respiratory failure	Baseline pulse oximetry and consideration of pulmonary imaging prior to lymphodepletion in patients with neutropenia or history of fungal disease During CRS, consider continuous pulse oximetry and/or pulmonary imaging in patients with respiratory symptoms Routine follow-up assessments, with repeat imaging in clinically indicated situations only
Ocular	Conjunctivitis Photophobia Vision changes and/or impairment Papilloedema Retinal detachment	Baseline clinical eye examination Ophthalmology consultation as clinically indicated In patients with a known history of ocular involvement from malignancy perform consultation prior to CAR T cell infusion
Renal	Acute kidney injury Electrolyte disturbances Atypical haemolytic uraemic syndrome Renal failure	Baseline urinalysis and laboratory assessments including electrolyte panel, creatinine and albumin Daily laboratory assessments during CRS, including electrolyte panel, creatinine, albumin and urinalysis Nephrology consultation as clinically indicated

Capturing the patient experience

Clinically meaningful improvements in patient reported quality of life scores were observed across **all measures** at month 3 after CD19 CAR infusion



Change from baseline in PedsQL and EQ-5D VAS

Laetsch TW, Lancet Oncol. 2019

Future Directions

- To establish standardized metrics of comprehensively monitoring for CAR T-cell toxicities and optimize outcomes beyond CRS
  - Leverage knowledge gained across new CAR T-cell constructs targeting diseases beyond B-cell malignancies
- Allow for cross-trial and cross-construct comparisons of toxicity profiles
- To establish clear basic, translational and clinical research efforts which will facilitate new investigations and collaborative efforts to systematically study CAR T-cell related adverse events

“Beyond the Storm” Consortium

- February 2019: Investigators from NCI, Seattle, CHOP and CHLA met at the BMT Tandem meeting to discuss how to comprehensively evaluate CAR T-cell toxicities beyond CRS in children and young adults

- Identified several key elements of CAR T-cell toxicities that needed further evaluation

- Established a collaborative network for information exchange, ultimately leading to the development of this conference

Beyond the Storm: Goals

- To foster a **collaborative exchange** of ideas and research efforts focused on the early experience with CAR T-cell related toxicities and late effects in children, beyond CRS
- To **establish** clear, **basic, translational and clinical research efforts** which will facilitate new investigations and collaborative efforts to systematically study CAR T-cell related adverse events
- To establish **biologic correlates**, standardized metrics for toxicity monitoring and intervention strategies to optimize post CAR T-cell management
- To **develop a foundation** upon which additional outcomes related to CAR T-cell therapies can be studies

Beyond the Storm: Archived Conference

Steering Committee

NCI:
- Nirali N. Shah
- Haneen Shalabi

CHOP:
- Stephan Grupp
- Allison Leahy

Boston Children's:
- Christine Duncan

Seattle:
- Rebecca Gardner
- Colleen Annesley
- Juliane Gust

CHLA:
- Michael Pulsipher
- Agne Taraseviciute

CIBMTR:
- Marcelo Pasquini

https://ncifrederick.cancer.gov/events/conferences/car-t-cell-therapy-beyond-storm

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Beyond the Storm Consortium

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