Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immune Effector Cell-related Adverse Events

August 12, 2021

5:30 – 6:30 p.m. EST

This webinar is supported, in part, by independent medical education grant funding from

AMGEN MERCK

(as of 6/7/21)

Webinar Agenda

5:30 – 5:35 p.m. ET	Overview: Welcome and Introductions
5:35 – 6:10 p.m. ET	Presentation and Discussion
6:10 – 6:25 p.m. ET	Question and Answer Session
6:25 – 6:30 p.m. ET	Closing Remarks

Webinar faculty

Stephen Grupp, MD, PhD – *Children's Hospital of Philadelphia and University of Pennsylvania*

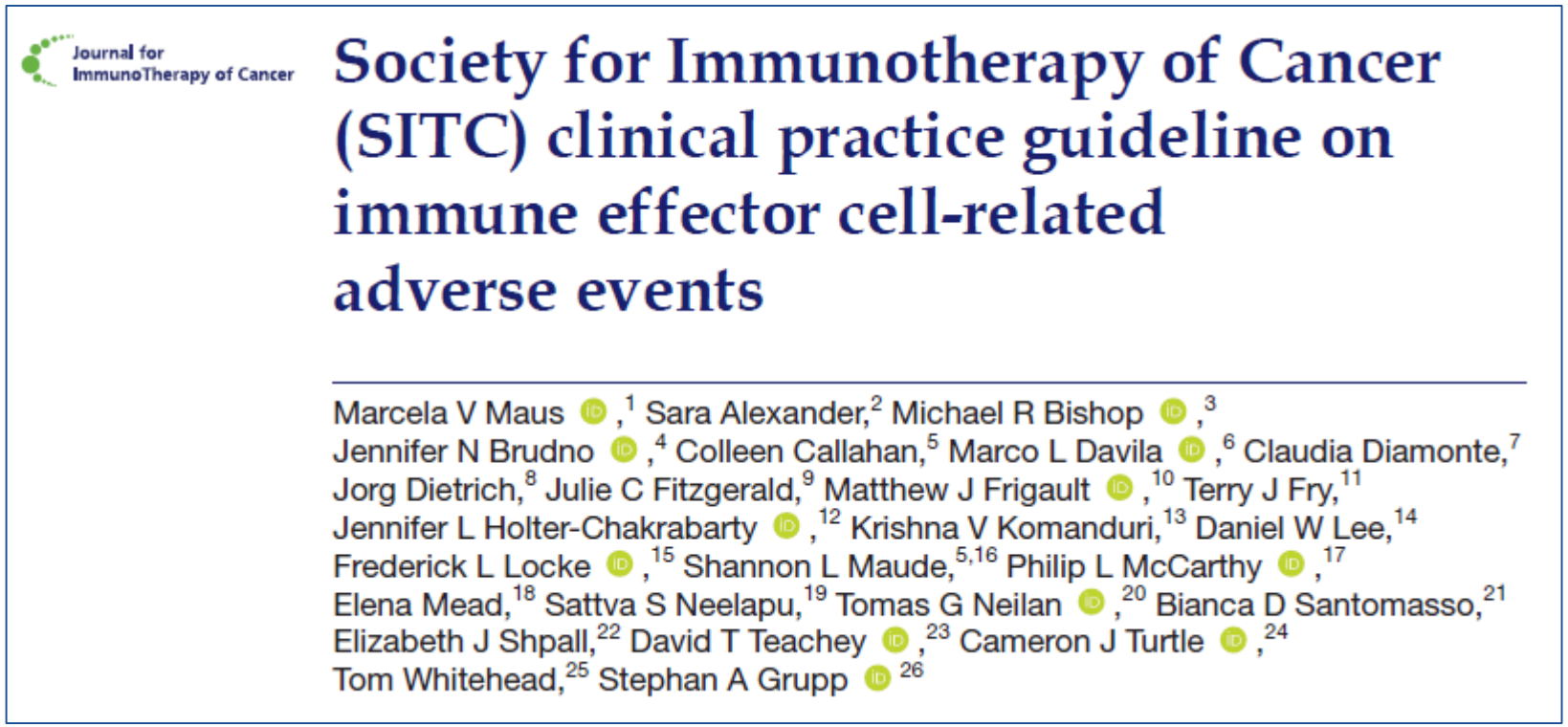
Sattva Neelapu, MD – *The University of Texas MD Anderson Cancer Center*

Jorg Dietrich, MD, PhD – *Massachusetts General Hospital*

Learning objectives

- Appropriately manage CAR T and immune effector cell-associated toxicities
- Outline risk factors for IEC-associated toxicities
- Describe ongoing studies for the management of IEC-related toxicities

Development of the guideline



Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events

Marcela V Maus [1], Sara Alexander,[2] Michael R Bishop [3], Jennifer N Brudno [4], Colleen Callahan,[5] Marco L Davila [6], Claudia Diamonte,[7] Jorg Dietrich,[8] Julie C Fitzgerald,[9] Matthew J Frigault [10], Terry J Fry,[11] Jennifer L Holter-Chakrabarty [12], Krishna V Komanduri,[13] Daniel W Lee,[14] Frederick L Locke [15], Shannon L Maude,[5,16] Philip L McCarthy [17], Elena Mead,[18] Sattva S Neelapu,[19] Tomas G Neilan [20], Bianca D Santomasso,[21] Elizabeth J Shpall,[22] David T Teachey [23], Cameron J Turtle [24], Tom Whitehead,[25] Stephan A Grupp [26]

Development of the guideline

- Panel of 26 members, including physician, nursing, and patient advocacy perspectives
- Representatives from several organizations participated:
  - American Society of Hematology (ASH)
  - American Society for Transplantation and Cellular Therapy (ASTCT)
  - Foundation for the Accreditation of Cellular Therapy (FACT) at the University of Nebraska Medical Center
  - Emily Whitehead Foundation
- All recommendations based on literature where available, and panel experience and consensus where applicable

FDA-approved CAR T therapies

Drug	Target/co-stimulatory domain	Indication
Axicabtagene ciloleucel	CD19/CD28	Adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, after 2+ therapies
Tisagenlecleucel	CD19/4-1BB	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse
Tisagenlecleucel	CD19/4-1BB	Adults with R/R large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma
Brexucabtagene autoleucel	CD19/CD28	Adults with R/R mantle cell lymphoma
Lisocabtagene maraleucel*	CD19/4-1BB	Adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma not otherwise specified (including arising from indolent lymphoma), high-grade B-cell lymphoma, PMBCL and follicular lymphoma grade 3B, after at least 2 prior therapies
Idecabtagene vicleucel*	BCMA/4-1BB	Adults with R/R multiple myeloma after 4+ prior therapies

**not approved at the time of Guideline publication*

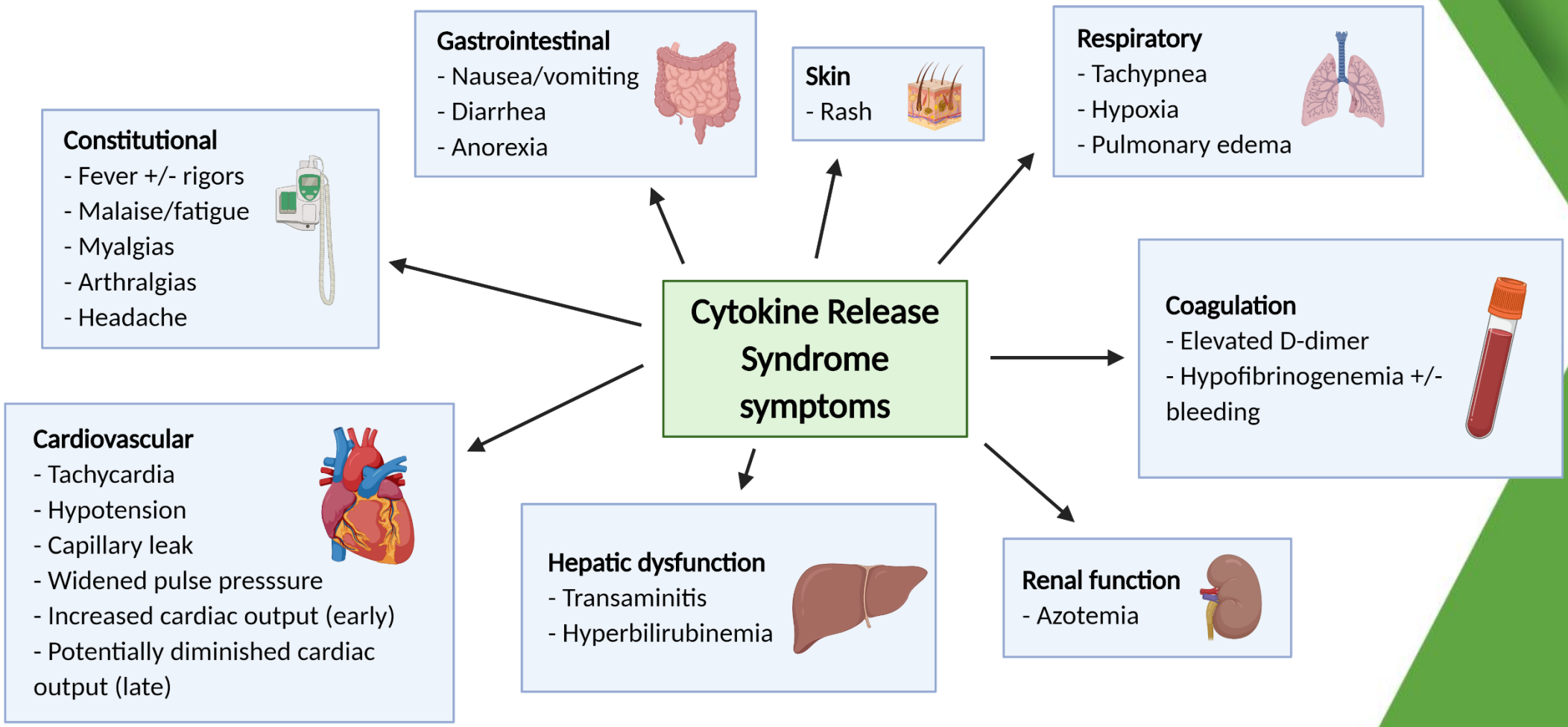
Webinar outline

- Management, risk factors and future directions for:

- CRS and related toxicities
  - Cardiovascular events
  - HLH/MAS

- Neurologic toxicities
  - ICANS
  - Cerebral edema

Cytokine release syndrome



ASTCT CRS grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38°C	≥ 38°C	≥ 38°C	≥ 38°C
with				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, non-rebreather mask or venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

Lee, Santomasso, Biol Blood Marrow Transpl 2018

Monitoring for CRS

- Events requiring physician notification include:
  - Deviations from baseline systolic blood pressure
  - Heart rate >120 or <60 bpm
  - Arrhythmia
  - Respiratory rate >25 or <12 breaths/minute
  - Arterial oxygen saturation <92% on room air
  - Upward trend in blood creatinine or liver function tests
  - Tremors or jerky movements in extremities
  - Altered mental status
  - Temperature ≥ 38°C

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Management of CRS

Grade 1	Grade 2	Grade 3	Grade 4	Tocilizumab-unresponsive	Tocilizumab + steroids-unresponsive
Close monitoring and supportive care	Consider tocilizumab	Tocilizumab	Tocilizumab + steroids	If CRS does not respond to 1 dose of tocilizumab, combine steroids + tocilizumab	Options include: Anakinra, siltuximab, HD methylprednisolone

- For **elderly patients or those with significant co-morbidities**, tocilizumab should be considered earlier in the treatment course.
- If CRS does not improve after tocilizumab + steroids, **infections** should be considered and managed appropriately.
- If steroids are used, a **rapid taper** should be employed once symptoms begin to improve.

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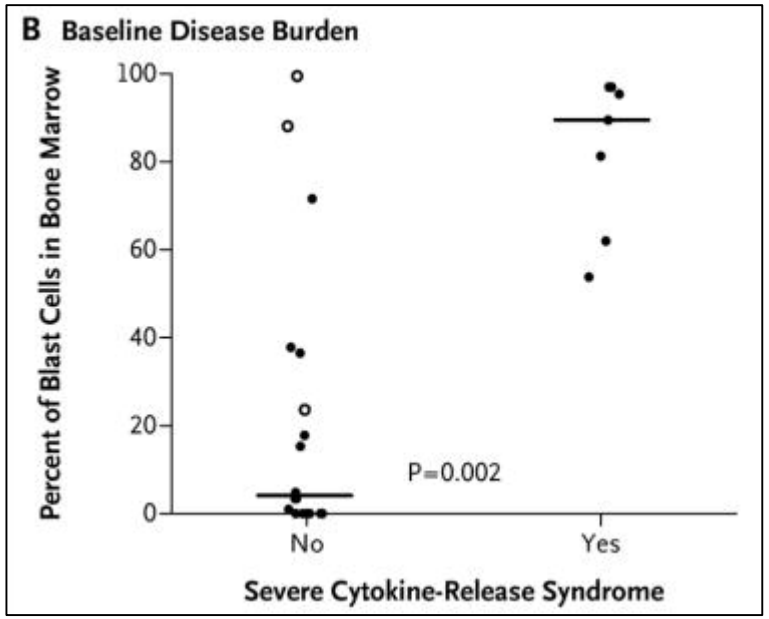
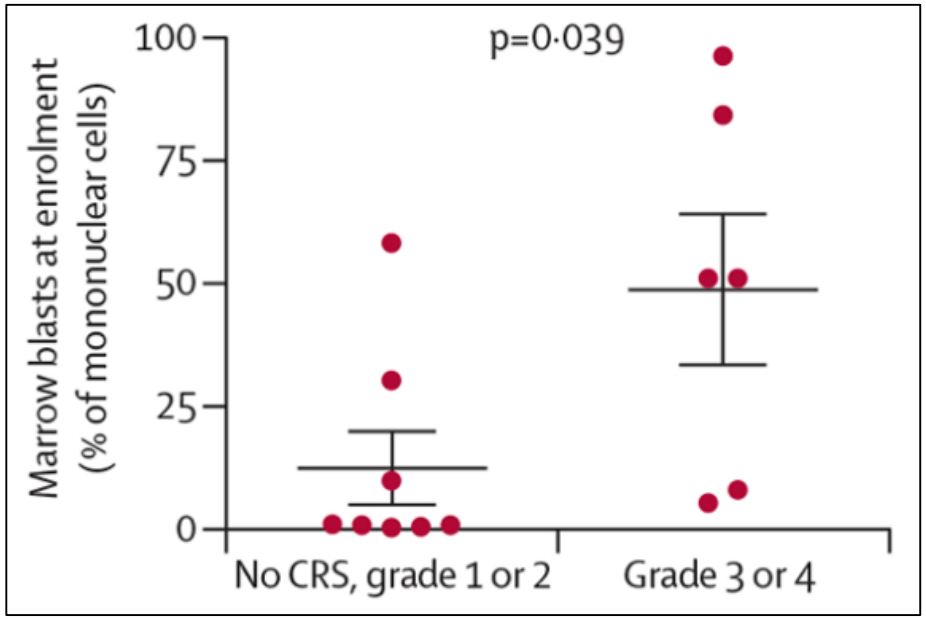
Risk factors for CRS

- High disease burden
- CD28 costimulatory domains in the CAR T product
- High dose of CAR T cells
- Pre-existing cardiac risk factors
- Baseline inflammatory state

CRS and high baseline tumor burden





Maude, N Engl J Med 2014
Lee, Lancet 2015

Trials for prevention/treatment of CRS

Trial	Study	Status	Inclusion criteria	Intervention
NCT02906371	A Two Cohort Pilot Study of Tocilizumab Optimization Timing for CAR-T19-Associated CRS Management in Pediatric Patients With CD19 Expressing Relapsed/Refractory B-cell ALL	Active, not recruiting Two cohorts, open-label, phase 1/2 study	Pediatric patients aged 1–24 years with CD19 expressing relapsed/refractory B-cell ALL	Two cohorts defined based upon pre-infusion high versus low tumor burden: 1. High tumor burden cohort (high risk of severe CRS) to receive earlier administration of tocilizumab for CRS 2. Low tumor burden cohort (low risk of severe CRS) to receive standard timing of tocilizumab for CRS
NCT04048434	Effectivity of Extracorporeal Cytokine Adsorption (Cytosorb) as Additive Treatment of CAR-T Cell-Associated Cytokine Release (CRS) Syndrome and Encephalopathy Syndrome (CRES)	Not yet recruiting	Patients aged 18 or older who develop severe CRS (>3)/severe CRES (>3) and CRS/CRES onset <6 hrs.	Patients with severe CAR-T cell-associated CRS (defined as vasopressor dependent) will be treated with standard of care + cytokine adsorption (6 hourly for 24 hrs.).
NCT03696784	A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing Inducible Caspase 9 Safety Switch (iC9-CAR19) in Subjects With Relapsed/Refractory B-cell Lymphoma	Recruiting Phase I	Patients aged 18 or older with relapsed or refractory B-cell Lymphoma	Patients who develop grade 4 CRS or grade ≥3 CRS or who develop grade ≥3 CRES or grade 2 CRES that is unresponsive to standard of care interventions will be given Rimiducid at 0.4 mg/kg.
NCT04071366	A Study of Itacitinib for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy	Study to open in January 2020 Phase 2	Patients 12 years and older eligible to receive either tisagenlecleucel or axicabtagene ciloleucel for approved hematologic indications	Oral administration of itacitinib 200 mg once daily for 30 days for the prevention of CRS

Murthy, Immunotargets Ther 2019

Cardiovascular toxicities

- Common events include:
  - Hypotension; heart failure (new or worsening); arrhythmias
- Baseline evaluation of cardiac function is important
  - TTE, serum troponin, and NT-proBNP/BNP
- Risk factors for cardiac events include:
  - Prior therapies (anthracycline)
  - Prior cardiac insult
  - Low ejection fraction
  - Arrhythmias

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Management of cardiovascular events

- Any evidence of cardiac toxicity should warrant escalation of treatment (IL-6 blockade, steroids)
- High-risk patients should receive in-patient treatment
- Can continue treatment with: beta blockers, angiotensin II receptor blockers, calcium channel blockers, ACE inhibitors
- Should discontinue antiplatelet agents if possible

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HLH/MAS

- Hemophagocytic lymphohistiocytosis / macrophage activation syndrome
- Appears to be more common with certain CAR T products
- Substantial overlap with CRS symptoms
- Late onset and tocilizumab refractoriness may indicate HLH/MAS
- Symptoms:
  - High fever, elevated ferritin and liver enzymes, pancytopenias
  - Elevated serum IFNγ, IL-10, sIL-2Rα, IL-6, IL-8, GM-CSF
  - Hepatosplenomegaly, lymphadenopathy, hemophagocytosis

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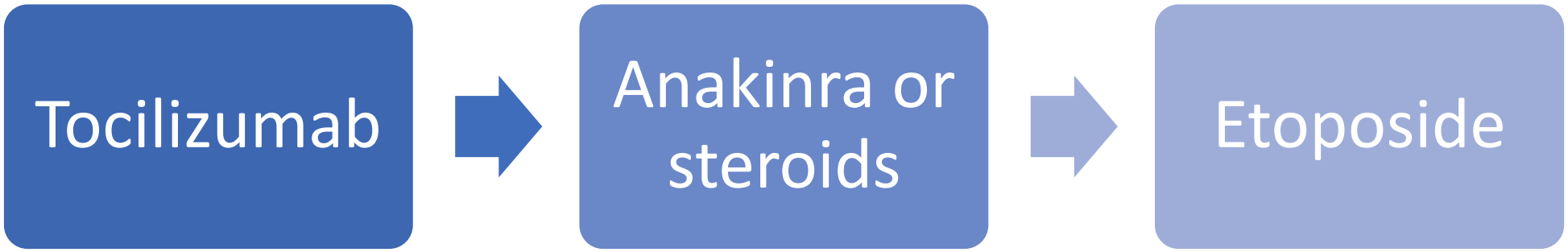
Management of HLH/MAS



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Webinar outline

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- Neurologic toxicities
  - ICANS
  - Cerebral edema

ASTCT ICANS grading - adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (patient is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Lee, Santomasso, Biol Blood Marrow Transpl 2018

ASTCT ICANS grading - pediatric

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score (age ≥12 years)	7–9	3–6	0–2	0 (patient is unarousable)
CAPD score (age <12 years)	1–8	1–8	≥9	Unable to perform CAPD
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), repetitive clinical or electrical seizures without return to baseline in between
Motor weakness (any age)	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Lee, Santomasso, Biol Blood Marrow Transpl 2018

Immune effector cell-associated encephalopathy (ICE) score

- **Orientation**: Orientation to year, month, city, hospital: 4 points (1 point each)
- **Naming**: Name 3 objects (e.g., clock, pen, button): 3 points (1 point each)
- **Following commands**: (e.g., Show me 2 fingers or close your eyes and stick out your tongue): 1 point
- **Writing**: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention**: Count backwards from 100 by 10: 1 point
- **Total scale**: 0-10

Monitoring for ICANS

- Altered mental status defines the onset of ICANS
- Work-up should include:
  - CRP
  - CBC
  - CMP
  - Fibrinogen
  - Prothrombin time test
  - PT/INR
- Head CT, EEG, and brain MRI may be considered

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Management of ICANS

- **4-1BB** CAR T agents: consider steroids at grade 2 ICANS; administer steroids for grades 3-4 ICANS
- **CD28** CAR T agents: administer steroids for grades 2-4 ICANS
- Management of neurotoxicity **may take precedence** over low-grade CRS, due to possibility of tocilizumab worsening ICANS
  - For example: in the case of a patient with concomitant grade 1 CRS (fever) and grade 2 ICANS, steroids should be given. This does not apply to higher-grade CRS.
- If **steroids** are used, administer at least two doses and employ a fast taper
- **Levetiracetam** is recommended for management of seizures

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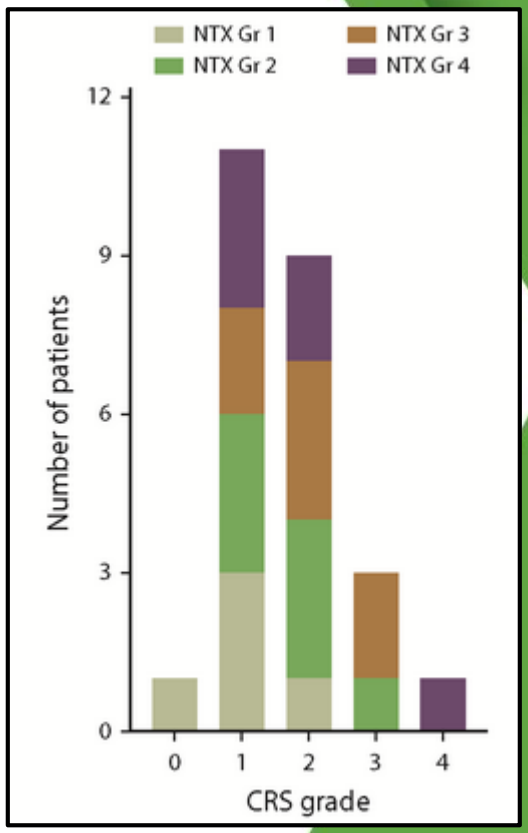
Risk factors for ICANS

- High tumor burden
- High CAR T dose
- High ferritin and cytokine levels
- Low platelet level
- High-grade CRS
- Pre-existing neurologic comorbidities
- Early fever after CAR T dosing



Karschnia, Blood 2019
Gust, Cancer Discov 2017

Risk factors for ICANS

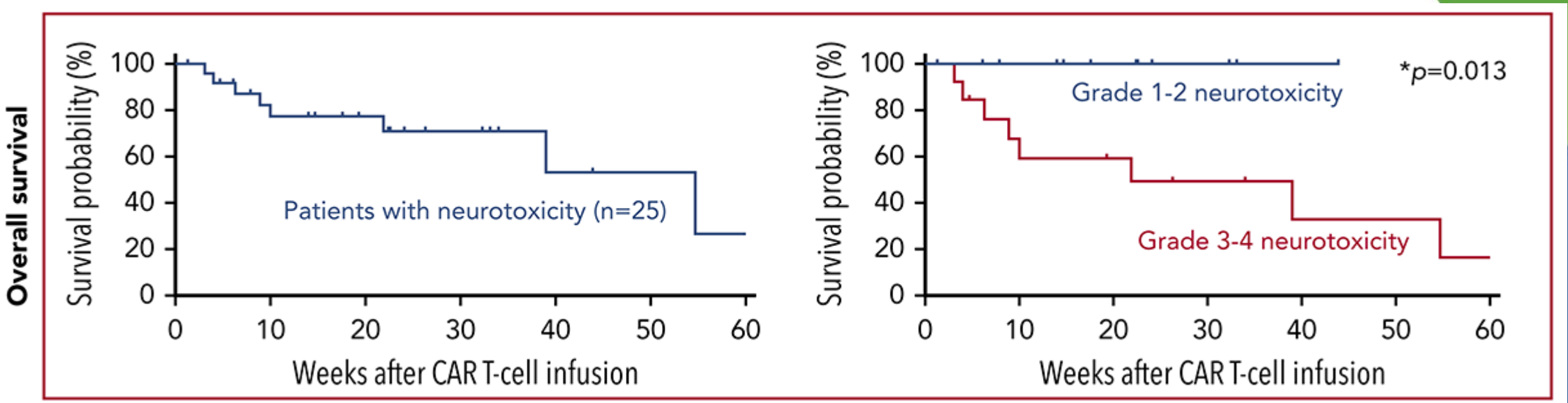
		Grade 0	Grade 1-2	Grade 3-5	Univariate	Multivariate
Age	<40 years	41	37	22	0.094	
	40-60 years	66	13	22		
	>60 years	64	17	19		
Pre-existing neurologic comorbidities	Any	45	28	28	0.0059	0.0023
Marrow disease %	Median (range)	0.6 (0-97)	0.4 (0-93)	25.8 (0-97)	0.072	0.0165
Lymphodepletion regimen	Cy/Flu	56	22	22	0.11	0.0259
	Non-Cy/Flu	76	7	17	<0.0001	0.0009
CAR T cell dose	$2x10^5$ cells/kg	57	29	14		
	$2x10^6$ cells/kg	64	17	19		
	$2x10^7$ cells/kg	42	0	58		
Cytokine release syndrome	None (Grade 0)	88	13	0	<0.0001	
	Grade 1-2	57	25	18		
	Grade 3-5	6	6	88		

Values as percent of patients unless otherwise indicated

Gust, Cancer Discov 2017

ICANS, steroid use and outcomes

- High-grade ICANS with prolonged steroid use >10 days appears to be a negative prognostic factor



Karschnia, Blood 2019

Cerebral edema

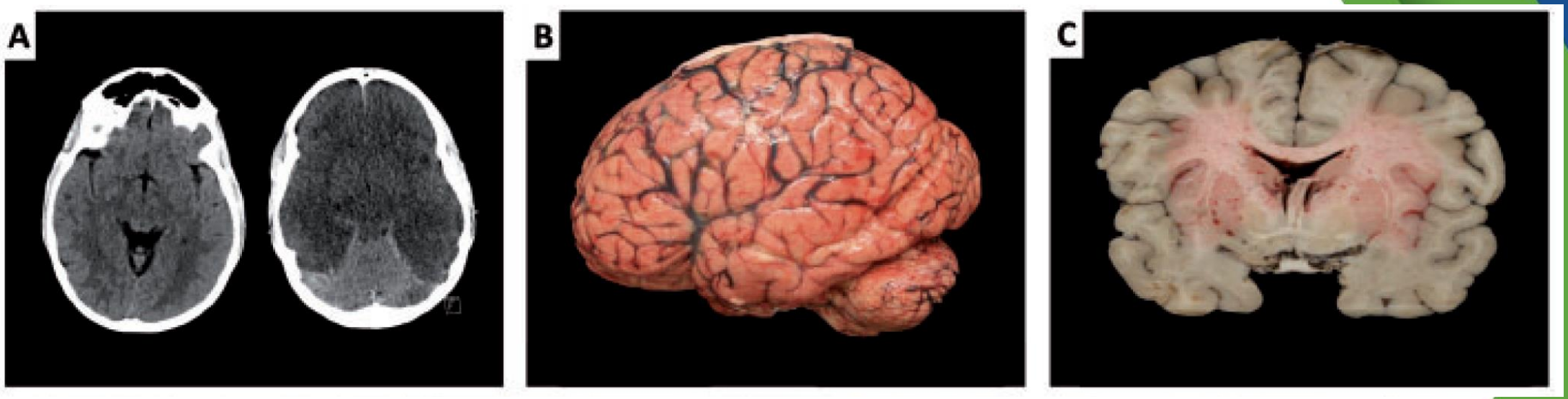
- Unclear whether ICANS and edema arise from distinct pathophysiology
- Disruption of the blood-brain barrier likely cause with capillary leakage syndrome
- Patients with suspected cerebral edema should be immediately referred to intensive care

June CH et al., Science, 2018

Management of cerebral edema

- Intensive Care Unit management
- Frequent Neuro checks
- Respiratory support
- Mannitol / Hyperventilation / Dexamethasone / hypertonic saline
- Consider EVD for ICP monitoring

Case: Fatal cerebral edema



21 M with relapsed B-cell ALL

- Cyclophosphamide/Fludarabine → CD-19 CAR-T
- Day 1: CRS grade 2 (fevers, tachycardia)
- Day 2: High-dose dexamethasone
- Day 4: Neuro exam abnormal with wordfinding difficulty → lethargic → unresponsive
- → intubated → Mannitol, Hyperventilation, Decadron → Repeated head CT
- Day 5: Declared brain death

Torre M et al, J Neuropath Exp Neurol, 2018

Conclusions

- The field of IEC toxicity management is rapidly changing, and guidelines may change accordingly
- Guidelines will be updated following new FDA approvals
- These guidelines can provide help for patient management, but clinical situations should include physician discretion
- Both CRS and ICANS can occur in the majority of patients, so familiarity with their presentation and management are important for all members of the cancer care team
- Prophylactic strategies are being explored in clinical trials

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Cancer Immunotherapy GUIDELINES

Case Studies in Immune Effector Cell-related Adverse Events

October 13, 2021, 5:30–6:30 p.m. ET

Immune Checkpoint Inhibitor-related Adverse Events Guideline Overview

August 13, 2021, 10–11 a.m. ET

CME-, CNE-, CPE-certified

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Acknowledgements

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Questions or comments: connectED@sitcancer.org

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