CLINICAL FORUM

Rapid Recognition and Management of T-Cell Therapy-Related Toxicities in B-Cell Lymphomas:

Crucial Updates for the Emergency Department

Provided by RMEI Medical Education, LLC

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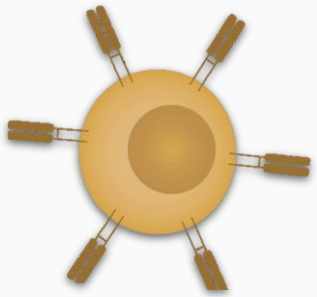
Supported by an educational grant from Genentech, a member of the Roche Group.

Agenda



Overview of T-cell Engaging Therapies for R/R B-Cell NHL

Improving Recognition in the ED

Managing Toxicity

Case Discussions

Overview

T-Cell Engaging Therapies for the Treatment of Relapsed/Refractory B-Cell Non-Hodgkin's Lymphoma

Jeremy S. Abramson, MD

B-Cell Non-Hodgkin's Lymphomas

NHL: Heterogenous group of B-cell and T-cell malignancies

Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) account for 20% to 30% of all adult NHLs. Others include CLL/SLL and MCL.

FL

Proliferates slowly but incurable in advanced stages. Can transform to more aggressive forms, including DLBCL.

DLBCL

Fast growing, aggressive NHL originating from mature B-cells. 30% to 40% of patients develop refractory disease or relapse.

B-Cell Non-Hodgkin's Lymphomas

The introduction of CAR T-cell therapy and bispecific antibodies (bsAbs) has transformed outcomes.

Cure Rates
(R/R DLBCL)

CAR-T:
Around 30% to 40%

BsAbs:
Not yet observed

Approximate ORR*
(R/R DLBCL)

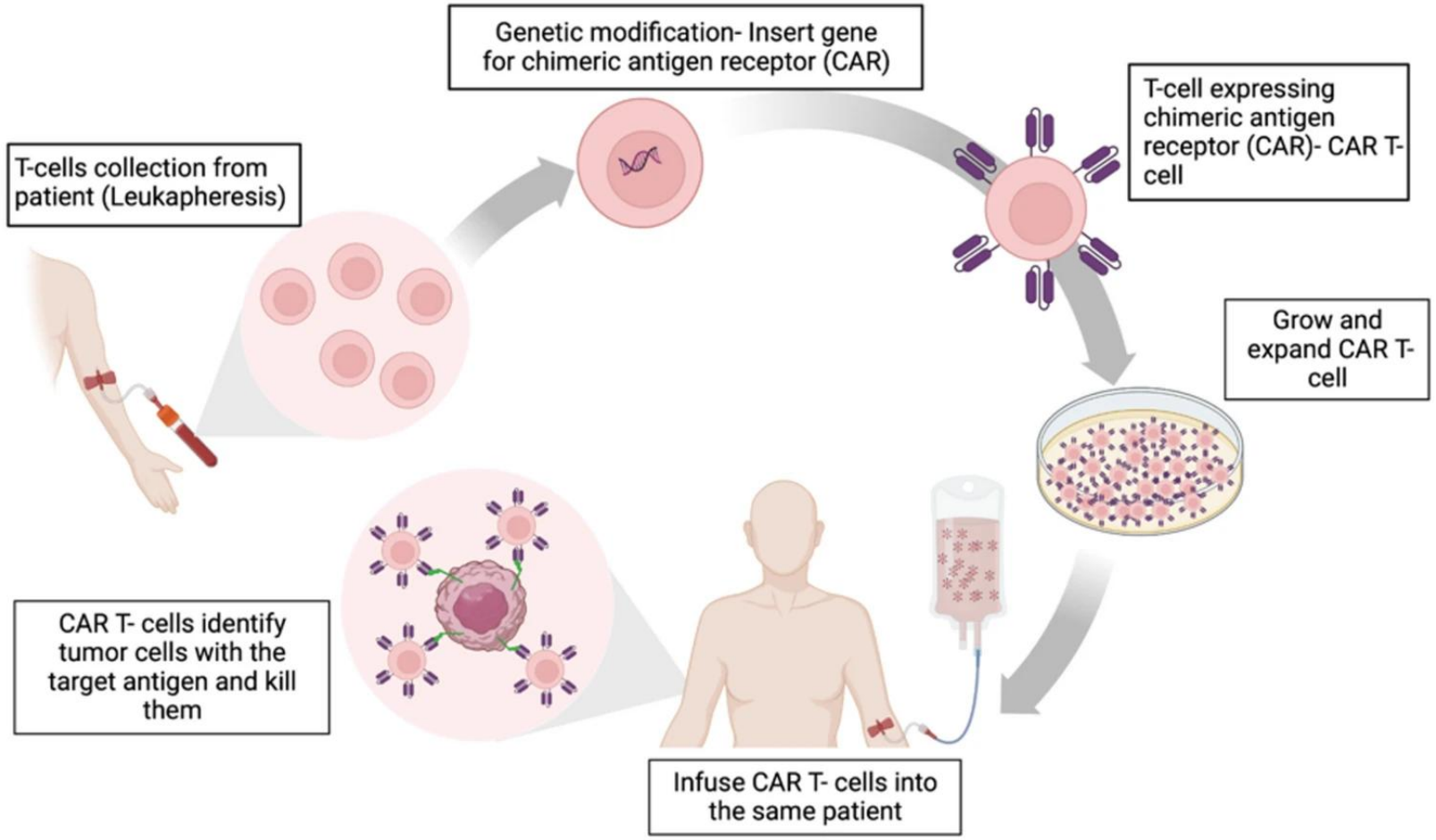
CAR-T:
Around 83%

BsAbs:
Around 63%

Mechanism of Action

CAR T-Cell Therapy

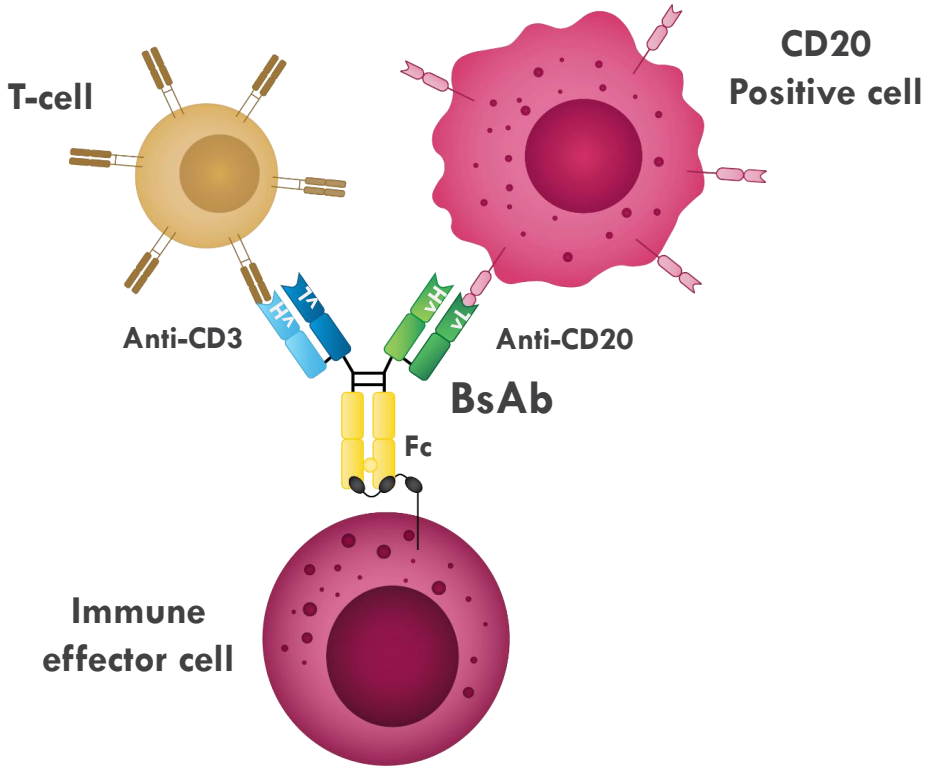
CAR T-Cells are "Bionic T-Cells"



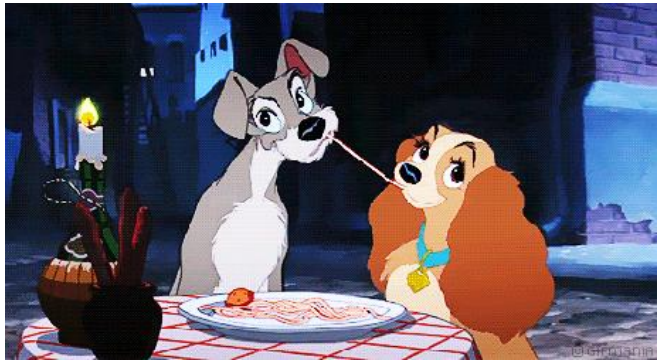
Mechanism of Action

Bispecific Antibodies

Bispecific Antibodies are the "Kiss of Death"



Bispecific antibodies bind **CD20 on tumor cells** and **CD3 on T cells,** bringing the 2 together. This then allows the T cell to initiate tumor cell lysis.



Analogy credit: Matthew Lunning, DO, FACP

Rampotas A, et al. *Ther Adv Hematol*. 2021;12:20406207211053120.
Falchi L, et al. *Blood*. 2023;141(5):467-480.

CAR T-Cell Therapy and BsAbs: Knowing the Differences

CAR T-Cell Therapy

Customized to patient	…*but* →	Manufacturing wait time
Single dose	…*but* →	Requires travel to specialized center and in-patient administration
Curative potential	…*but* →	More AEs and AE severity

Bispecific Antibodies

"Off-the-shelf" availability	…*but* →	Not customized, but an option for frailer patients not candidates for CAR-T
Outpatient administration*	…*but* →	Chronic administration
Less AEs and AE severity	…*but* →	No evidence of cure; useful in CAR-T R/R cases

Available T-Cell Engaging Therapies for B-NHL

Agent	Type	Indication	Route	First Approval (US)
Axicabtagene ciloleucel	Anti-CD19 CAR T with CD28 co-stimulation	• R/R LBCL • R/R FL	IV	2017
Tisagenlecleucel	Anti-CD19 CAR T with 4-1BB co-stimulation	• R/R DLBCL • R/R FL	IV	2017
Brexucabtagene autoleucel	Anti-CD19 CAR T with CD28 co-stimulation	• R/R MCL	IV	2020
Lisocabtagene maraleucel	Anti-CD19 CAR T with 4-1BB co-stimulation	• R/R LBCL • R/R FL • R/R CLL/SLL • R/R MCL	IV	2021
Mosunetuzumab	CD20 x CD3 bispecific antibody	• R/R FL	IV	2022
Epcoritamab	CD20 x CD3 bispecific antibody	• R/R DLBCL • R/R FL	SC	2023
Glofitamab	CD20 x CD3 bispecific antibody	• R/R DLBCL	IV	2023

NCCN Recommendations for T-Cell Engaging Therapies in DLBCL

2nd line, no transplant intention

CAR T-cells recommended

Lisocabtagene maraleucel

For 2nd line, when relapse after <12 months or primary refractoriness

CAR T-cells recommended

Axicabtagene ciloleucel
Lisocabtagene maraleucel

3rd line and subsequent therapy

CAR T-cells recommended

Axicabtagene ciloleucel
Lisocabtagene maraleucel
Tisagenlecleucel

Bispecifics recommended

Epcoritamab
Glofitamab

For progression after CAR T-cell therapy

Bispecifics recommended

Epcoritamab
Glofitamab

Zelenetz AD, et al. NCCN Guidelines: B-Cell Lymphomas. Version 3.2024; 26 Aug 2024.

NCCN Recommendations for T-Cell Engaging Therapies in FL

For 3rd and subsequent line therapy

Bispecifics recommended

- *Epcoritamab*
- *Mosunetuzumab*

CAR T-cells recommended

- *Axicabtagene ciloleucel*
- *Lisocabtagene maraleucel*
- *Tisagenlecleucel*

Zelenetz AD, et al. NCCN Guidelines: B-Cell Lymphomas. Version 3.2024; 26 Aug 2024.

Major Adverse Events Typical of T-Cell Engaging Therapies

CRS

Cytokine Release Syndrome

Surge in cytokines causing an acute, systemic inflammatory syndrome. Characterized by **fever,** may include hypotension, headache, tachypnea, tachycardia, rash, hypoxia, and/or organ dysfunction.

ICANS

Immune Effector Cell-associated Neurotoxicity Syndrome

Neurologic toxicity characterized by delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and rarely, cerebral edema

Others

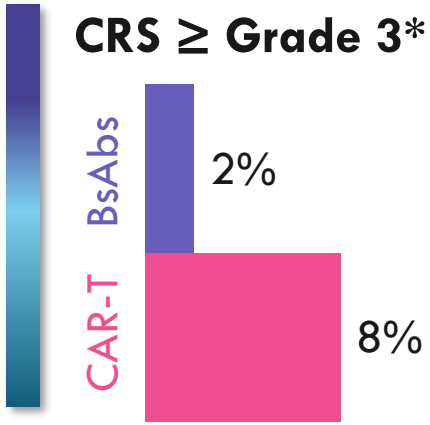
Tumor Flare, Cytopenias, Infections

Tumor flare reaction, cytopenias, and infectious complications, such as febrile neutropenia, urinary tract infections, pneumonia, and COVID-19

Major Adverse Events Typical of T-Cell Engaging Therapies

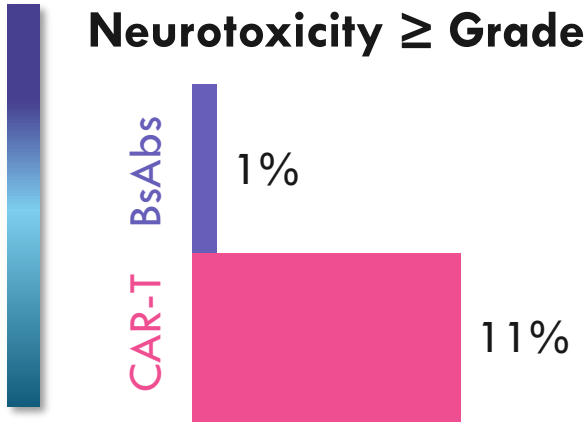
CRS

Cytokine Release Syndrome



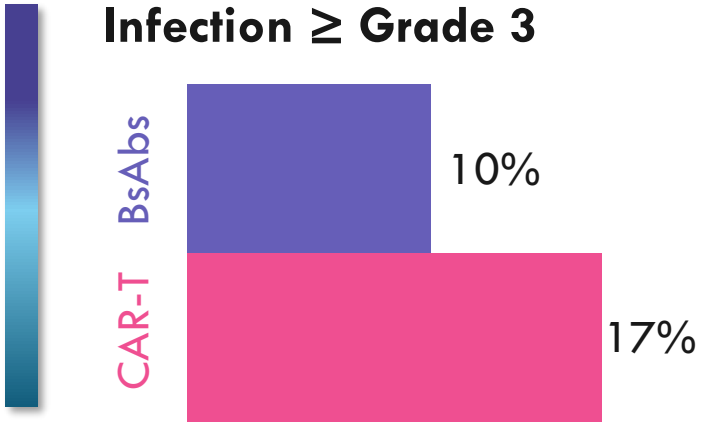
ICANS

Immune Effector Cell-associated Neurotoxicity Syndrome



Others

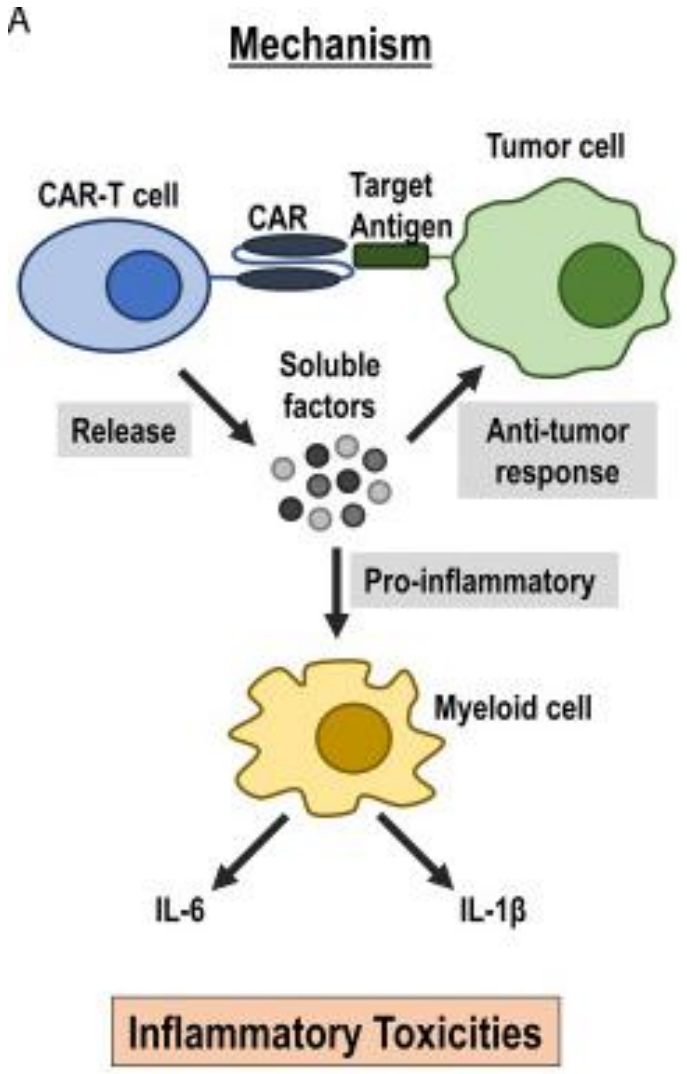
Tumor Flare, Cytopenias, Infections



*Incidence and severity of CRS and ICANS varies widely by CAR T agent: Axi-cel and brexu-cel have a much higher incidence than liso-cel and tisa-cel.

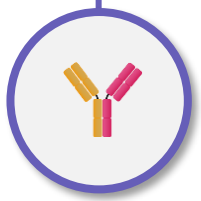
Mechanism of AE Development: CAR T-Cells

1. Chimeric antigen receptor (CAR) engages target antigen on tumor cell
2. Soluble factors released
3. Soluble factors assist anti-tumor response but may activate bystander myeloid cells.
4. Activated, myeloid cells secrete inflammatory cytokines (eg, IL-6, IL-1beta)
5. Characteristic inflammatory toxicities ensue



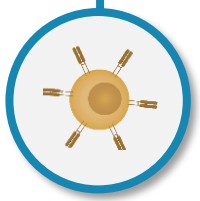
Mechanism of AE Development: Bispecific Antibodies

1. **Binding**



BsAbs bind to antigen on target cell surface

2. **Activation**



Immune and non-immune cells are activated

3. **Inflammation**

Inflammatory cytokines released in immense quantities causing AEs

Adverse Events Related to T-Cell Therapies

Improving Recognition in the Emergency Department

Jeremy S. Abramson, MD

Agenda

CRS

Symptoms and Severity Grading

ICANS

Symptoms and Severity Grading

Guidelines for Toxicity Recognition, Grading, and Management

Toxicity Recognition and Grading[1]

Characterizes CRS, ICANS, and grading systems. Used for CAR T and BsAbs.

American Society for Transplantation and Cellular Therapy (ASTCT) consensus guidelines, 2019

CAR T-Cell Toxicity Management Guidelines[2]

*Focused on CAR T-cells**

SITC	2020
ASCO	2021
EBMT/EHA	2022
NCCN	2024

*Were extrapolated to bsAb before specific guidelines were issued by ASH in 2024

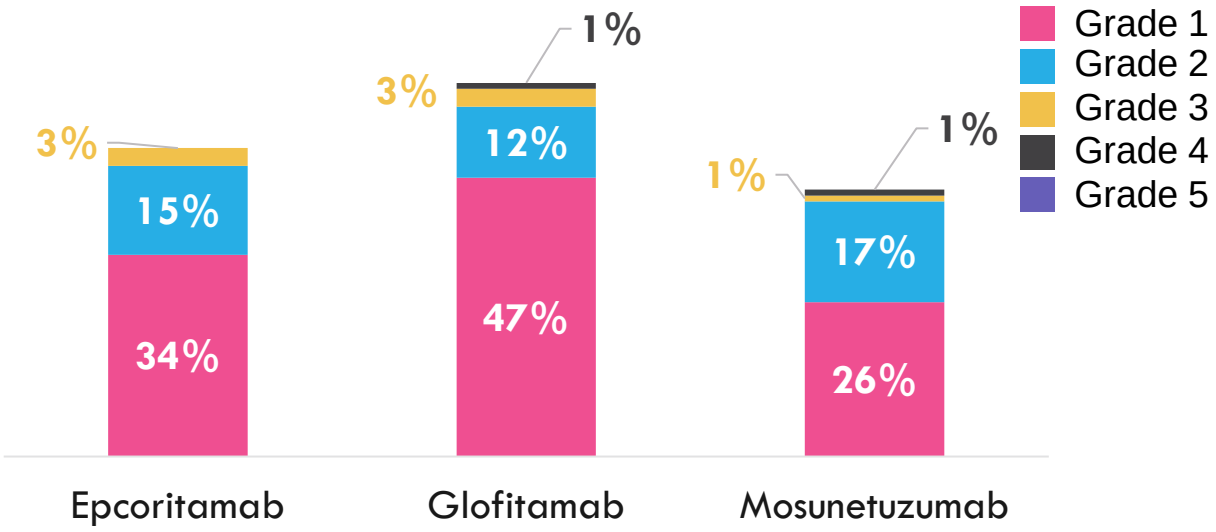
American Society of Hematology[3]

Focus: BsAbs Toxicity Management

Consensus Recommendations on the Management of Toxicity Associated with CD3×CD20 Bispecific Antibody Therapy

Nature of AEs with BsAbs

CRS Rates for BsAbs, by Grade



	Grade 1-2	Grade 3-4
ICANS	Up to **5%**	Up to **3%**

Median Duration of CRS

0.5 hours to 3 days

CRS: Quick Onset

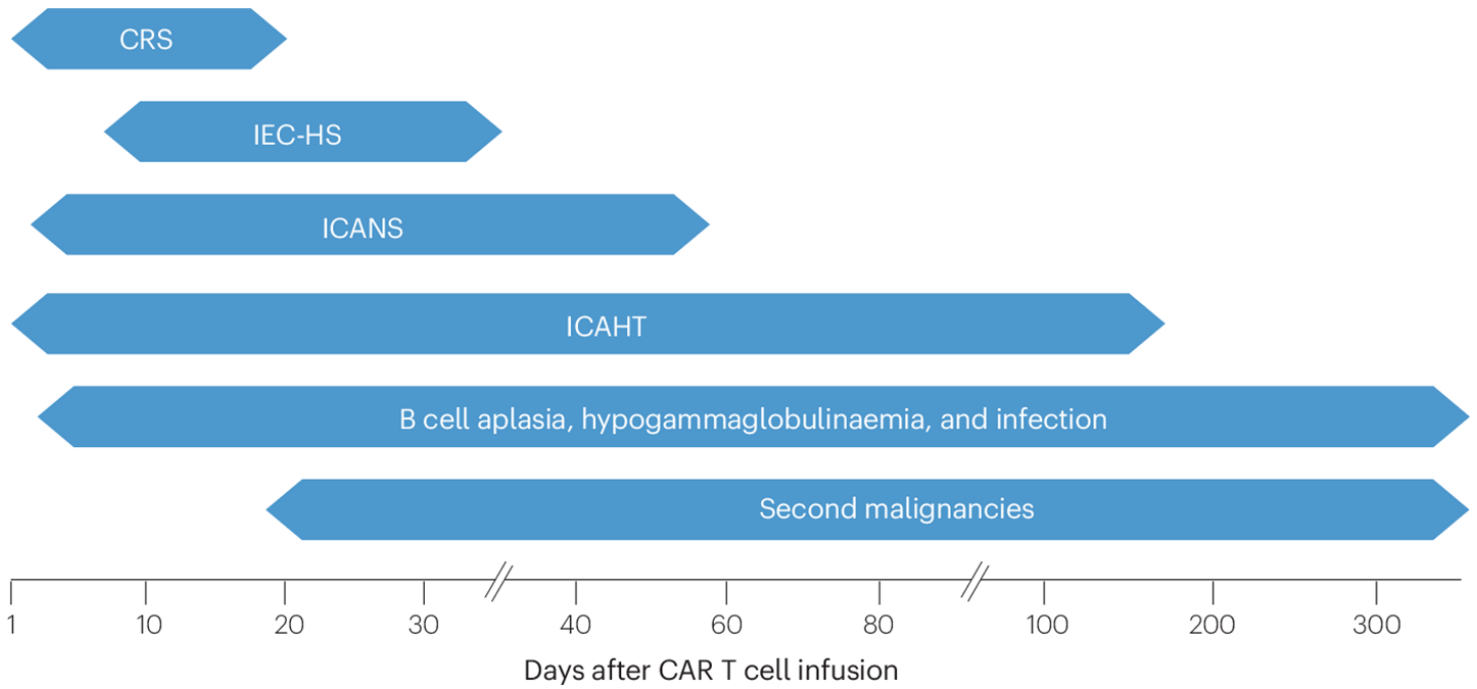
CRS typically occurs within hours to days after dosing

CRS Usually Occurs Early

CRS typically occurs in the first 1 to 2 months of therapy

Nature of CAR T-Cell Associated AEs

Timeline



CRS, cytokine-release syndrome; ICAHT, immune effector cell-associated hematotoxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome

Onset Time

- Typically occurs within 14 days of infusion
- Median onset time: 2 to 7 days after infusion

High-grade CRS can begin just hours after CAR T-cell infusion

First Presenting Sign

Fever often marks onset and is most frequently the first presenting sign of CRS

Modified from: Brudno JN, et al. *Nat Rev Clin Oncol*. 2024;21(7):501-521.

Nature of CAR T-Cell Associated AEs

Disease	Product	Line	Toxicity			
			CRS (%)	Neurologic (%)	Cytopenia	Infection
LBCL	Axi-cel	3+	13	28	78	Not included
		2	6	21	69	14
	Liso-cel	3+	2	10	60	12
		2	1	4	80	15
		NTE	2	5	48	7
	Tisa-cel	3+	22	12	39	20
FL	Axi-cel	3+	6	15	33	5
	Tia-cel	3+	0	1	32	5
	Liso-cel	3+	1	2	58	14
MCL	Brexu-cel	2+	15	31	85	32
	Liso-cel	3+	1	9	56	15

CRS Definition

"A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction."

CRS: Symptoms

Systemic

Fever
Rigors
Chills

Organ Failure

Organ dysfunction
Multi-organ failure
Acute kidney injury
Hepatic insufficiency
Transaminitis

Pulmonary/ Respiratory

Hypoxia
Dyspnea
Pleural effusion

Cardiovascular

Hypotension
Sinus tachycardia
Capillary leak
Reduced cardiac ejection fraction
Arrythmia
Heart block
QTc prolongation

Hematologic

Coagulopathy

CRS-related deaths have been reported with several CAR T-cell products and are usually due to respiratory failure, cardiac arrest, multi-organ failure, or secondary hemophagocytic lymphohistiocytosis.

Risk Factors for CRS with CAR T-Cells[1]*

- High nodal and/or bone marrow burden of malignancy
- Poor ECOG-PS
- Elevated pretreatment levels of serum inflammatory markers
- Low baseline platelet counts
- Receipt of and/or requirement for bridging therapy
- More intensive lymphodepleting chemotherapy
- High CAR T-cell doses
- High peak blood levels of CAR T-cells
- Leukemic phase disease
- Elevated LDH

*Patient- and disease-related risk factors for toxicity from CD3XCD20 bispecific antibodies have not been characterized.[2]

CRS Grading: ASTCT

CRS Severity is Determined by Hypotension and Hypoxia

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vaso-pressor 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, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities can be graded according to CTCAE v5.0 but do not influence CRS grading.

*Patients who receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): Definition

"A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema."

Calculating Immune Effector Cell-Associated Encephalopathy Score

Points	Domain	
●●●●	**Orientation**	*Orientation to year, month, city, hospital*
●●●	**Naming**	*Ability to name 3 objects*
●	**Following Commands**	*Ability to follow simple commands*
●	**Writing**	*Ability to write a standard sentence*
●	**Attention**	*Ability to count backwards from 100 by 10*

ICE Scoring

Score	ICANS Grade
10	No Impairment
7 to 9	Grade 1
3 to 6	Grade 2
0 to 2	Grade 3
0*	Grade 4

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
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 nonconvulsive 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; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ASTCT ICANS Consensus Grading for Children (<12 Years Old): CAPD Score

Answer the following questions based on interactions with the child over the course of the shift					
	Never, 4	Rarely, 3	Sometimes, 2	Often, 1	Always, 0
1. Does the child make eye contact with the caregiver?					
2. Are the child's actions purposeful?					
3. Is the child aware of his/her surroundings?					
4. Does the child communicate needs and wants?					
	Never, 0	Rarely, 1	Sometimes, 2	Often, 3	Always, 4
5. Is the child restless?					
6. Is the child inconsolable?					
7. Is the child underactive; very little movement while awake?					
8. Does it take the child a long time to respond to interactions?					

CAPD Guidance for Patients Aged 1 to 2

Original	Guidance for Patients Aged 1 to 2
1. Does the child make eye contact with the caregiver?	Holds gaze, prefers primary parent, looks at speaker
2. Are the child's actions purposeful?	Reaches and manipulates objects, tries to change position, if mobile may try to get up
3. Is the child aware of his/her surroundings?	Prefers primary parent, upset when separated from preferred caregivers, comforted by familiar objects (ie, blanket, stuffed animal)
4. Does the child communicate needs and wants?	Uses single words or signs
5. Is the child restless?	No sustained calm state
6. Is the child inconsolable?	Not soothed by usual comforting actions, eg, singing, holding, talking, or reading
7. Is the child underactive; very little movement while awake?	Little, if any play, efforts to sit up, pull up, and if mobile, crawl or walk around
8. Does it take the child a long time to respond to interactions?	Not following simple directions, if verbal, not engaging in simple dialog with words or jargon

ASTCT ICANS Consensus Grading for Children

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for children age ≥12 years	7 to 9	3 to 6	0 to 2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children age <12 years	1 to 8	1 to 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; stupor or coma
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive 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	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

Patient Education and ED Presentation

Patients are instructed by their oncology teams to monitor for:

CRS

Temperature
Blood Pressure
Heart Rate
Oxygen Levels

ICANS

Confusion
Difficulty with speech
Difficulty staying awake
Abnormal actions
Seizures

Patients may present to ED if:

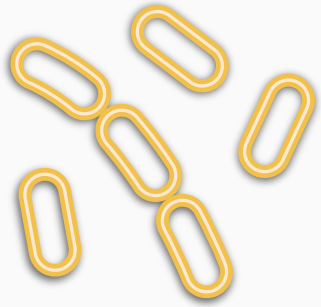
- Temperature ≥100.4°F
- Pulse Ox ≤90% or >5% change from baseline
- Decrease in SBP >10 mmHg from baseline and/or SBP <90 mmHg
- Increased HR >110 or more than 20 bpm from baseline while at rest
- Change in thinking or speech

Managing Toxicity

Current Recommendations

Joshua Brody, MD

Agenda

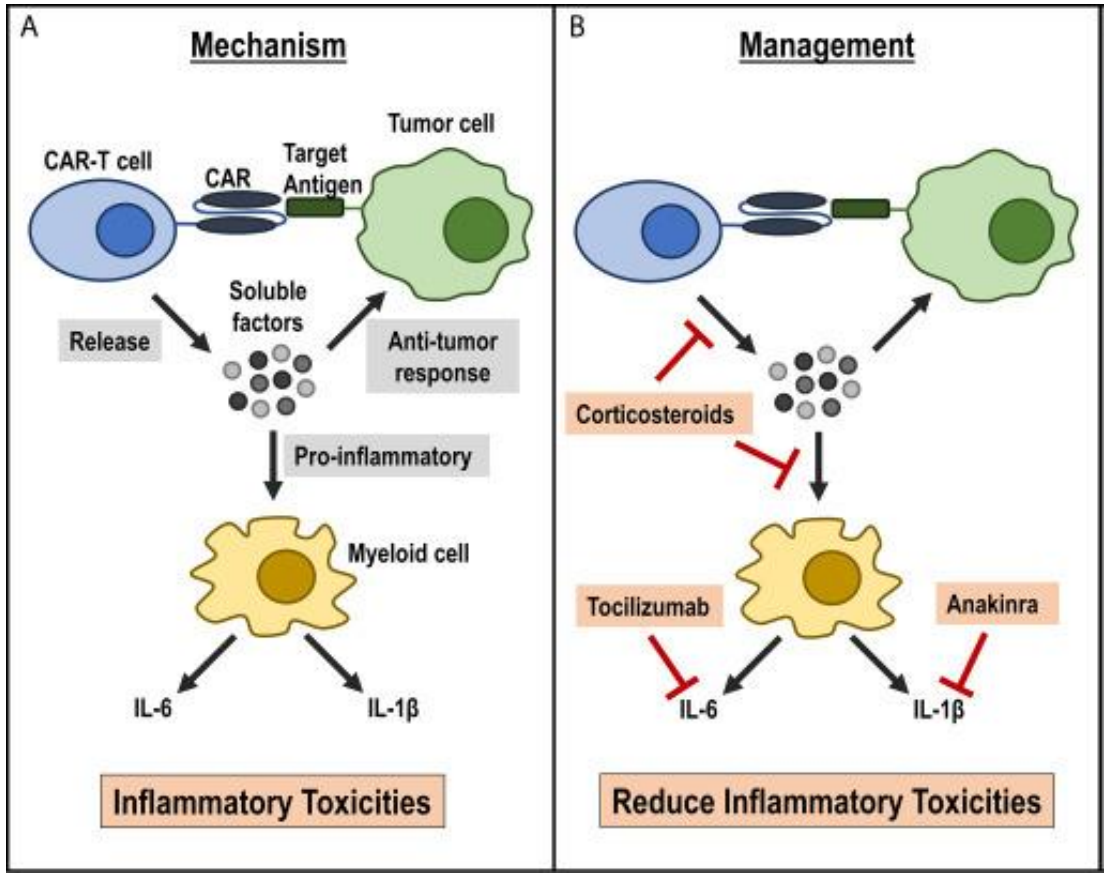


CRS Management

ICANS Management

Management of Other Toxicities

Principle Behind Management Strategy



CRS Management: NCCN Guidelines (CAR T)

CRS Grade	Anti-IL-6 Therapy	Steroids
1	For prolonged CRS (>3 days) in patients or those with significant symptoms, comorbidities, and/or are >65 years, consider 1 dose of IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg)	For idecabtagene and lisocabtagene, consider IV dexamethasone 10 mg every 24 hours for early-onset CRS (<72 h after infusion)
2	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose); repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1 to 2 doses of anti-IL-6 therapy; consider IV dexamethasone 10 mg every 12 to 24 hours depending on product
3	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6 to 12 hours depending on the product. If refractory, manage as Grade 4
4	Anti-IL-6 therapy as per Grade 2 if maximum dose not reached within 24-hour period	IV dexamethasone 10 mg every 6 hours; if refractory, consider 3 doses of IV methylprednisolone 1 to 2 g/day depending on the product; if refractory, consider dosing every 12 hours: other lines of therapy may be considered

CRS Management: Bispecifics

Workup and Evaluation

- History and physical, including vitals and evaluation of respiratory symptoms
- Review medications
  - BsAb received, last dose of antipyretic therapy, steroids, or anti-cytokine administration
- Assess for neurotoxicity
- Assess for alternate diagnosis
  - For example, infection, VTE, respiratory infection, volume overload or dehydration, and exacerbation of underlying cardiopulmonary condition
- For duration of symptoms >1 week, consider excluding HLH/MAS

CRS Management: Bispecifics

Grade	Acetaminophen	Dexamethasone	Anti-IL-6
1	(Home) 650 to 1000 mg PO	10 mg once (if refractory or recurrent fever)	• Tocilizumab if protracted fever (>48 h despite steroids) • Early tocilizumab if pt has multiple risk factors
2	650 to 1000 mg as needed, up to 3 to 4 times daily	10 mg q 12 h	• Tocilizumab if symptoms persist despite IV fluids and dexamethasone (~4 to 6 h after dosing) or if clinically unstable • Consider alternative if persistent symptoms despite maximal dosing
3	1000 mg IV as needed up to 3 to 4 times daily when safe	(eg, 10 mg IV Q 6 h), until resolution to grade ≤1, followed by taper	• Administer tocilizumab and consider alternative agent if persistent Grade 3 CRS despite maximal dosing
4	1000 mg IV as needed up to 3 to 4 times daily when safe	(eg, 20 mg IV every 6 h), until resolution to grade ≤1, followed by taper	• Administer tocilizumab and if repeated doses of tocilizumab have been used, consider alternative agent if persistent Grade 4 CRS despite maximal dosing of first agent

ICANS

Grade	Level of Care	Dexamethasone	Anti-Epileptics	Anakinra
1	Pending clinical scenario and social situation, can consider observation or close monitoring in outpatient setting	Can consider dexamethasone 10 mg once		
2	Admit for monitoring	Dexamethasone 10 mg IV every 12 h, followed by taper once grade ≥1		
3	ICU + Neurology Consult	Dexamethasone 10 mg IV every 6 h, followed by taper once grade ≥1	As needed for seizure management	Consider adding anakinra 100 mg every 12 h if symptoms persist beyond 24 h, continue until resolution
4	ICU + Neurology Consult			

BsAbs: Tumor Flare Reaction

What is it?

Short-term volumetric increase in lymphoma lesions

Signs/Symptoms

Erythema, pain, and fever, and can result in local compression or organ dysfunction

When

Occurs most frequently after the first dose or first target dose of a BsAb, and may occur together with other symptoms of CRS

Frequency

Rare

Management

- Irradiation of high-risk site may be considered in certain cases if there is concern for vital organ compromise
- Monitor closely
- Consider inpatient drug administration
- Consultations, as appropriate
- Tumor flare reaction typically responds rapidly to corticosteroids

Other Toxicities with BsAbs

Cytopenias

- Growth factor support can be considered for neutropenia
- Consider withholding bsAb per label
  - May continue if cytopenia is disease-related (e.g., marrow infiltration by lymphoma)

Tumor Lysis Syndrome

Risk is no different from other therapies. TLS risk assessment should follow current standards for patients with lymphomas.

Infections

- Withhold treatment if there is an active infection
- Prophylaxis against *Pneumocystis jirovecii* pneumonia and varicella-zoster virus is universally recommended
- Although vaccine response may be impaired, standard vaccinations (including flu and COVID-19) are recommended as indicated

Case Discussions

Addressing AEs Related to T-Cell Therapies: Practical Considerations for the ED

James

A 62-year-old male with a history of relapsed DLBCL presents to the ED with acute onset of high fever, chills, and shortness of breath. He has been receiving treatment with a bsAb for the past 2 weeks and his most recent dose was ~48 hrs ago.

- T: 39.5°C
- BP: 90/60 mmHg
- O_2Sat: 88% (room air)
- RR: 28 bpm | HR: 110 bpm

Discussion

Initial Stabilization Strategy

What's on the Differential?

Determining CRS Grade

ED Management Strategy

Care Coordination

Gulnar

A 58-year-old female with refractory FL presents to the ED with acute onset confusion, severe headache, and difficulty speaking after receiving CAR T-cell therapy 3 weeks ago.

- Difficulty recognizing family members and following commands
- Difficulty speaking, finding words
- Seizure witnessed by family, lasting approximately 2 minutes
- T: 38.5°C, BP: 160/95 mmHg

Discussion

- Initial Stabilization Strategy
- What's on the Differential?
- Determining ICANS Grade
- ED Management Strategy
- Care Coordination

Thank you!

Please do not forget to take the
post-test and complete the **evaluation** to receive credit.