CAR-T Cells: Learning How to Deal with Complications

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Disclosures

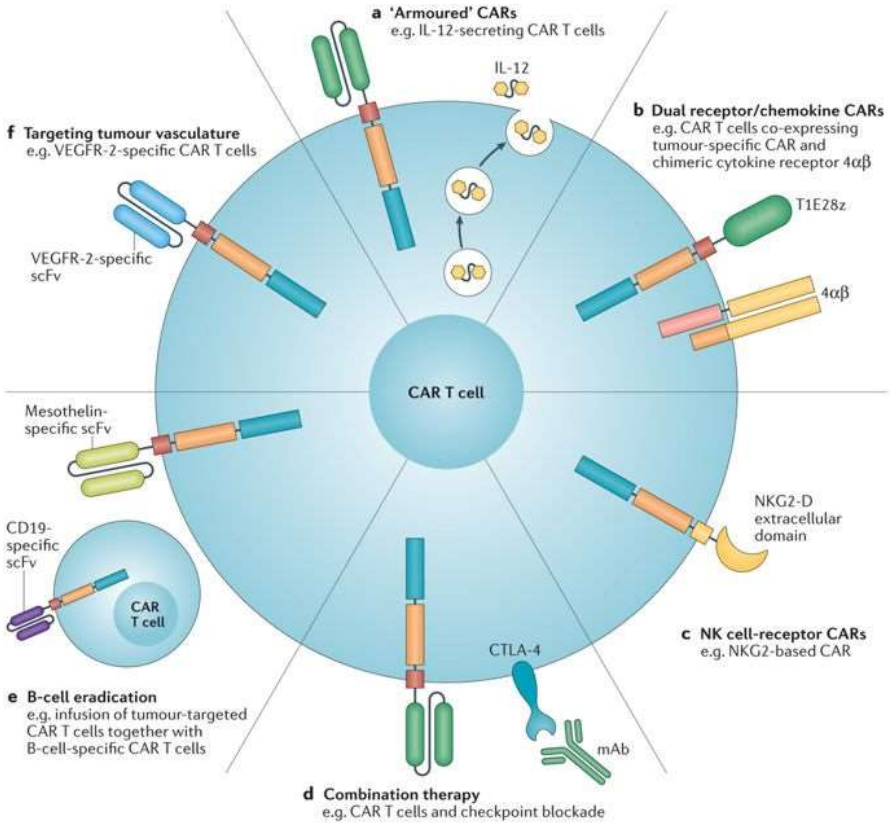
I have no relevant financial or other conflicts of interests to disclose.

Objectives

- Describe available Chimeric Antigen Receptor (CAR)-T cell therapies
- Recognize signs and symptoms of common serious adverse effects associated with CAR-T cell therapies
- Review recommended supportive care interventions and monitoring for patients receiving CAR-T cell therapy

Chimeric Antigen Receptor T Cells

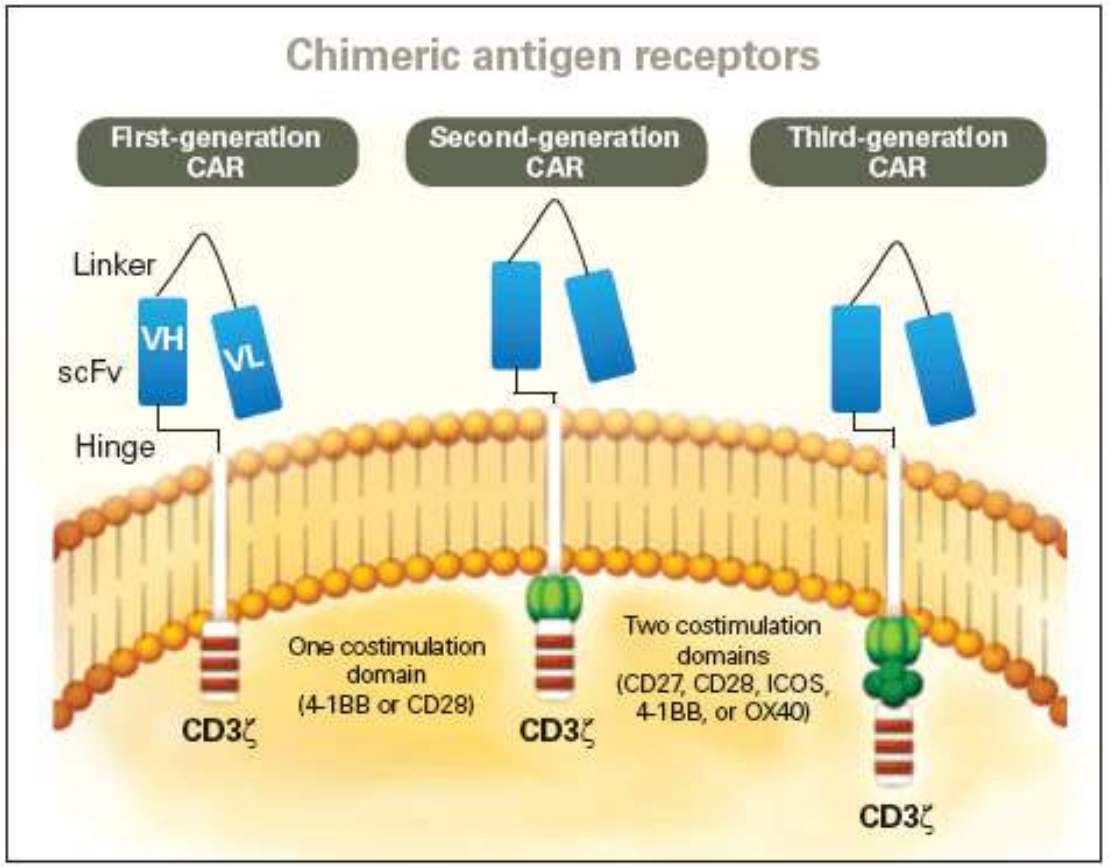
- Genetically modified T cells which bind to tumor surface antigens
- Many targets in development
  - CD19
  - CD20
  - CD22
  - CD33
  - B-cell maturation antigen (BCMA)



Jackson HJ et al Nat Rev Clin Oncol 2016(13):370-383.

Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

Structure



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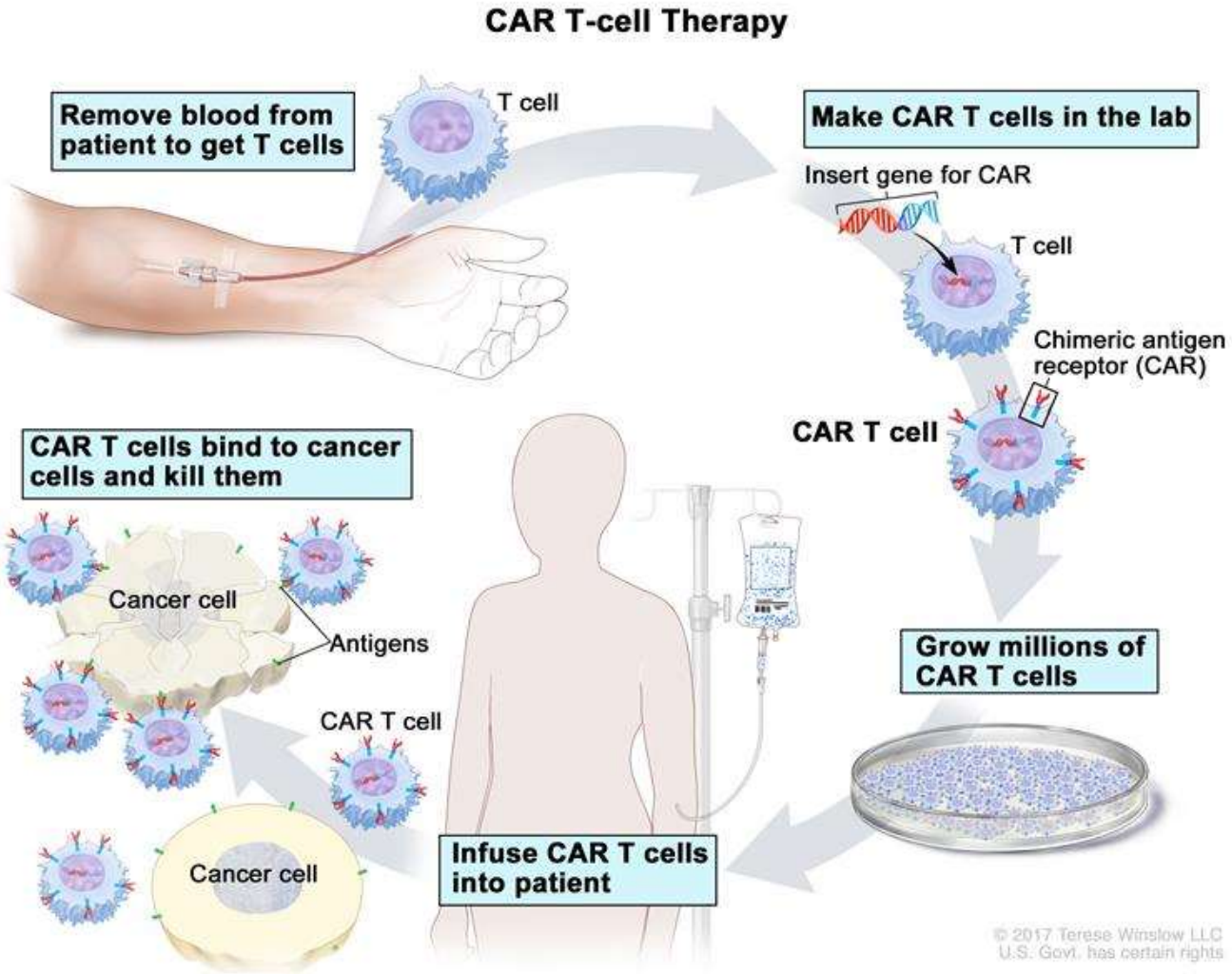

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy

FDA Approved CD19 CARs

- Tisagenlecleucel (CTL019)
  - Pediatric and young adults up to 25 years old with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL)
  - Adults with relapsed or refractory large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

- Axicabtagene ciloleucel (Axi-cel)
  - Adults with relapsed or refractory large B-cell lymphoma after two or more systemic lines of therapy, including DLBCL-NOS, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

Efficacy

	Tisagenlecleucel		Axicabtagene Ciloleucel
	B-Cell Acute Lymphoblastic Leukemia	Diffuse Large B-Cell Lymphoma	Diffuse Large B-Cell Lymphoma
Primary Clinical Trial	ELIANA (n=75)	JULIET (n=93)	ZUMA-1 (n=101)
Overall Response Rate	61 (81%)	48 (52%)	84 (83%)
Complete Response	45 (60%)	37 (40%)	59 (58%)
Secondary Endpoints	RFS: 80% (6 months), 59% (12 months) OS: 19.1 months	RFS: 74% (6 months) PFS: NR (responders) OS: 12 months	PFS: 5.9 months (all patients), Not reached (responders) OS: NR

RFS = relapse free survival
OS = overall survival
PFS = progression free survival
NR = not reached

Maude SL et al. N Engl J Med 2018;378:439-48.
Schuster SJ et al. N Engl J Med 2019;380:45-56.
Locke FL et al. Lancet Oncol 2019;20:31-42.

Selected Toxicities

Cytokine release syndrome (CRS)

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Hemophagocytic lymphohistiocytosis (HLH/MAS)

Other toxicities of special interest

- Febrile neutropenia
- Prolonged cytopenias (>28 days)
- Infection
- Hypotension
- Tumor lysis syndrome

Cytokine Release Syndrome

- Most common toxicity of cellular immunotherapy
- Onset typically within 1 week of cell infusion
- Pathophysiology via activation of T cells resulting in release of cytokines and chemokines
  - IL-2, soluble IL-2Rα, IFNγ, IL-6, soluble IL-6R, and GM-CSF

- Risk factors for severe CRS
  - High tumor burden
  - Early onset CRS (≤3 days of infusion)
  - Higher CAR-T cell dose
  - Intensity of lymphodepleting regimen
  - Comorbidities, older age
  - Infection
  - Inflammation
  - Thrombocytopenia

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CRS & Organ Toxicity

Cardiac	• Tachycardia, arrhythmias, heart block • Impaired left ventricular ejection fraction
Respiratory	• Dyspnea, tachypnea, hypoxia • Pleural effusion, pulmonary edema
Gastrointestinal	• Nausea, vomiting, anorexia, diarrhea
Hepatic	• Elevated AST and/or ALT • Hyperbilirubinemia
Renal	• Decreased urine output, increased serum creatinine • Acute kidney injury, may require dialysis
Dermatological	• Acneiform or maculopapular rash
Coagulopathy	• Disseminated intravascular coagulation • Prolonged PT and PTT and low fibrinogen, bleeding

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Cytokine Release Syndrome

	Tisagenlecleucel		Axicabtagene Ciloleucel
Occurrence	Any grades: 58 (77%)* Grade 3: 16 (21%)* Grade 4: 19 (25%)*	Any grade: 64 (58%)* Grade 3: 15 (14%)* Grade 4: 9 (8%)*	Any grade: 101 (94%)^ Grade 3: 14 (13%)^ Grade 4: 6 (20%)^
Median time to onset	3 days (range, 1-22)	3 days (range, 1-9)	2 days (range, 1-12)
Median time to resolution	8 days (range, 1-26)	7 days (range, 2-30)	7 days (range, 2-58)
ICU Admission for CRS	35 (47%)	(24%)	--
Median stay in ICU	7 days (range, 1-34)	--	--
High-dose vasopressors	19 (25%)	6 (6%)	--
Oxygen supplementation	33 (44%)	22 (24%)	--
Mechanical ventilation	10 (13%)	7 (7%)	--
Dialysis	7 (9%)	5 (5%)	--
Tocilizumab	28 (37%)	13 (14%)	--

*Grading by Penn criteria
^Grading by Lee criteria

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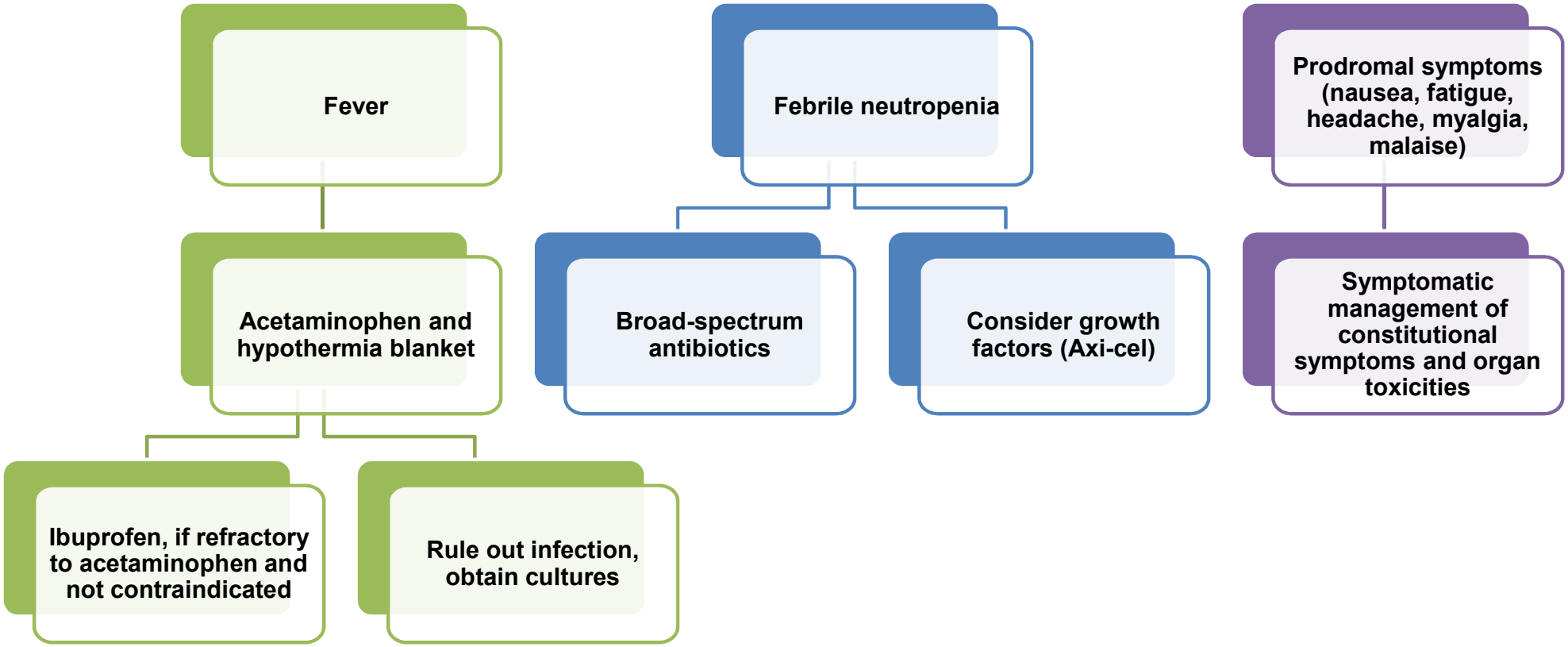
ASBMT Consensus Grading: CRS

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 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#, facemask, nonbreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)
Assess and grade organ toxicity separately per CTCAE v5.0				

*In patients who have CRS and receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
^CRS grading is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.
#Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

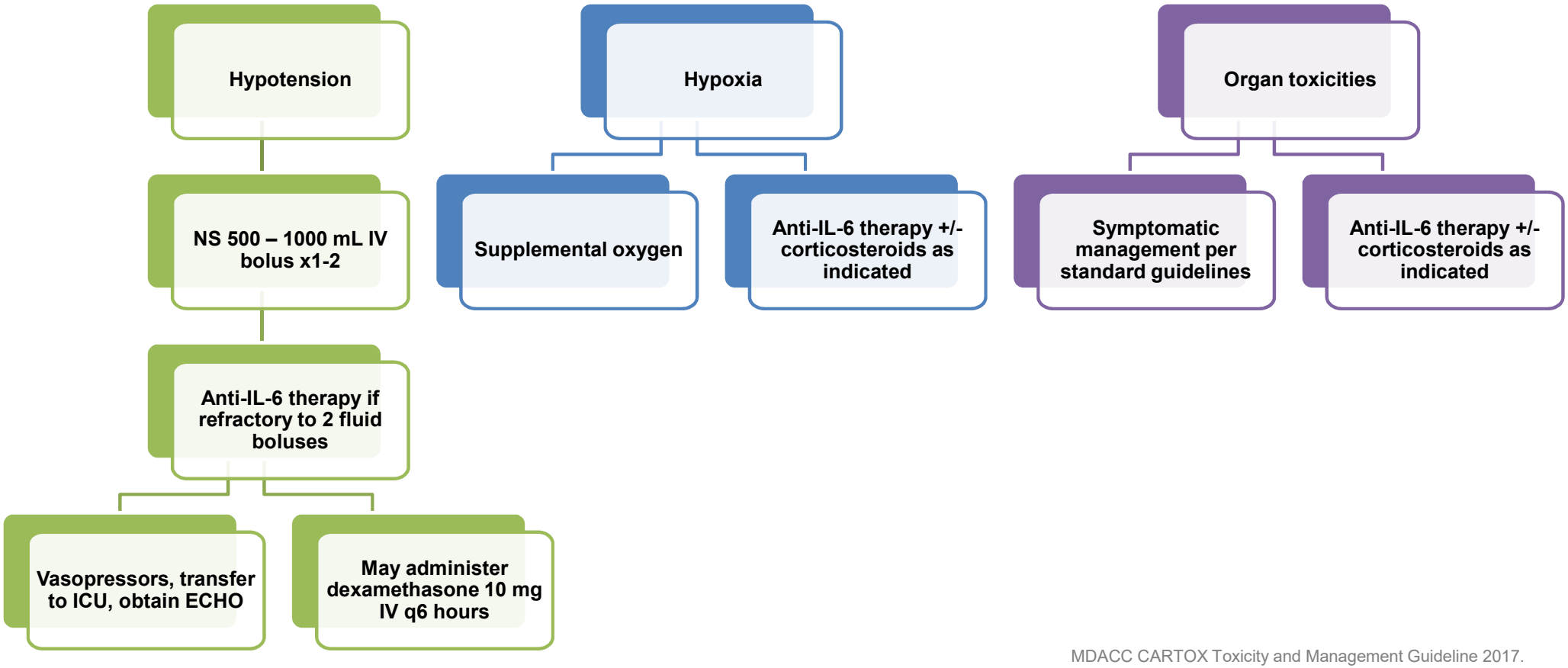
Lee DW et al. Biol Blood Marrow Transplant 2018;S1083-8791(18)31691-4.

CRS Management: Grade 1



MDACC CARTOX Toxicity and Management Guideline 2017.
Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

CRS Management: Grade 2



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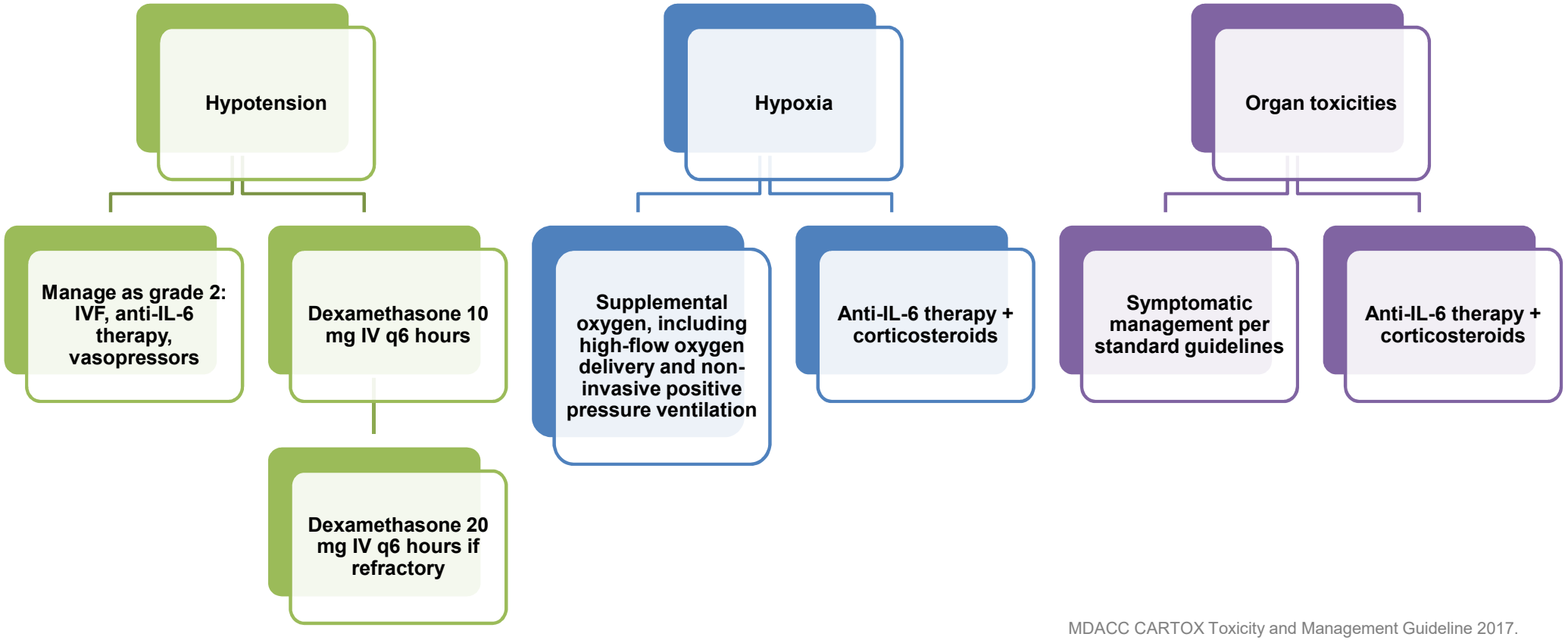
CRS Management: Grade 3



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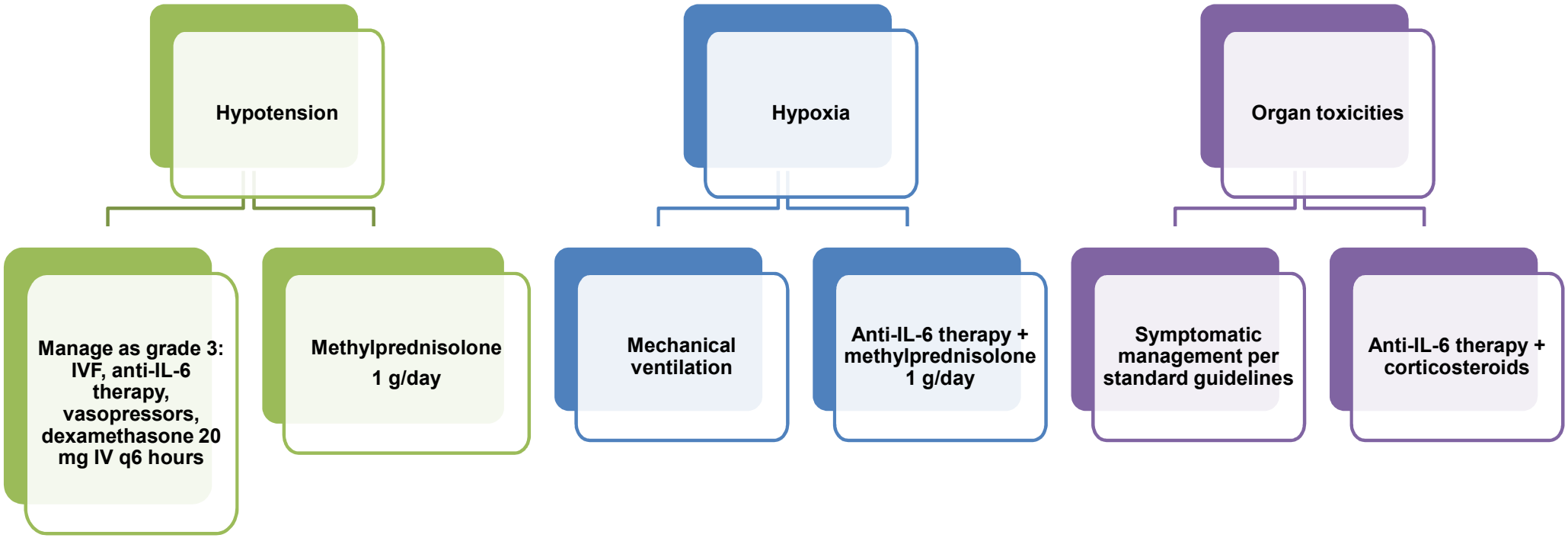
CRS Management: Grade 4



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Anticytokine Therapy

- Tocilizumab FDA-approved for use in severe or life-threatening CRS from CAR-T therapy
- Siltuximab may have improved efficacy in ICANS

Agents	Dosing	Administration	Precautions
Tocilizumab	Weight < 30 kg: 12 mg/kg/dose Weight ≥ 30 kg: 8 mg/kg/dose (Max 800 mg/dose; Max 4 doses total)	IV over 1 hour q8 hours for up to 3 doses/24-hour period	BBW: Infection, Tuberculosis Other AEs: Hepatotoxicity, hematologic toxicity, GI perforation, hypersensitivity/infusion reactions (polysorbate 80)
Siltuximab	11 mg/kg once (Max 1 dose/3-week period)	IV over 1 hour	Edema, pruritus, rash, GI perforation, hypersensitivity reactions

MDACC CARTOX Toxicity and Management Guideline 2017.

Corticosteroids

- Suppress inflammatory response
- Short course may not affect CAR T cell expansion
- Methylprednisolone versus dexamethasone superiority not known

Agents	Dosing	Comments
Dexamethasone	10-20 mg IV x1 dose or q6 hours	Frequency of dosing depends on severity of symptoms and response
Methylprednisolone	1 mg/kg q12 hours	May be used in place of dexamethasone for ICANS
High-dose methylprednisolone	500 mg IV q12 hours x 3 days, then 250 mg IV q12 hours x 2 days, then 125 mg IV q12 hours x 2 days, then 60 mg IV q12 hours until improvement to grade 1, then taper dose over 2 weeks	Can be stopped without tapering in patients with improvement to grade 1 or less within less than 1 week

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Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

- Formerly known as CAR-T cell related encephalopathy syndrome (CRES)
- Pathophysiology not well defined
  - Passive diffusion of cytokines into brain
  - T cell trafficking into the CNS
- Manifestation may be biphasic

Early (~5 days after cell infusion)	Late (~3 weeks after cell infusion)
• Concurrent with CRS and high fever • Tremor, dysgraphia, mild difficulty with expressive speech (naming objects), impaired attention, apraxia, lethargy • May respond to anti-IL-6 therapy	• Occurs as CRS is resolving • Seizures, confusion, encephalopathy • Anti-IL-6 generally not effective

- Risk factors for severe neurotoxicity
  - Tumor burden
  - ≥ Grade 3 CRS
  - Platelets < 60,000 cells/μL
  - Peak CAR-T expansion at day 7
  - Peak cytokines at day 3 (GM-CSF, IFNγ, IL-15, IL-5, IL-10, IL-2)

Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.
Park JH et al. J Clin Oncol 2017;:7024-7024.

Neurotoxicity

	Tisagenlecleucel		Axicabtagene Ciloleucel
Indication	B-Cell Acute Lymphoblastic Leukemia	Diffuse Large B-Cell Lymphoma	Diffuse Large B-Cell Lymphoma
Occurrence	Any Grade: 49 (72%)* Grade ≥3: 14 (21%)*	Any grade: 62 (58%)* Grade ≥3: 19 (18%)*	Any grade: 94 (87%)* Grade ≥3: 35 (32%)*
Most common events	Headache 37% Encephalopathy 34% Delirium 21% Anxiety 13% Sleep disorders 10% Dizziness 6% Tremor 9% Peripheral neuropathy 4%	Headache 21% Encephalopathy 16% Delirium 6% Anxiety 9% Sleep disorders 9% Dizziness 11% Tremor 7% Peripheral neuropathy 8%	Encephalopathy 57% Headache 44% Tremor 31% Dizziness 21% Aphasia 18% Delirium 17% Insomnia 9% Anxiety 9%
Median time to onset	6 days	6 days	4 days (range, 1-43)
Median time to resolution	6 days	14 days	17 days

*Grading by CTCAE v4.03

Maude SL et al. N Engl J Med 2018;378:439-48.
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Locke FL et al. Lancet Oncol 2019;20:31-42.

ASBMT Consensus Grading: ICE Score

Immune Effector Cell-Associated Encephalopathy (ICE)	Points
Orientation to year, month, city, hospital: 4 points	4
Ability to name 3 objects (e.g. point to clock, pen, button): 3 points	3
Ability to write a standard sentence	1
Ability to count backwards from 100 by 10	1
Ability to follow simple commands (e.g. “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1

ICE Score:
10 = No impairment
7-9 = Grade 1
3-6 = Grade 2
0-2 = Grade 3
If patient unarousable and unable to perform ICE assessment = Grade 4

Lee DW et al. Biol Blood Marrow Transplant 2018;S1083-8791(18)31691-4.

ASBMT Consensus Grading: ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	Patient unarousable, unable to perform ICE
Depressed consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulation	Patient 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); or 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

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Neurotoxicity Management

Grade 1: Observation and Evaluation

- Supportive care, aspiration precautions, IV hydration
- Swallow evaluation – if impaired, withhold/convert oral intake of food, medicine, fluids, nutrition
- Avoid CNS depressants – can give low-dose lorazepam or haloperidol for agitation
- Neurology consultation
- Fundoscopic exam to assess for papilledema
- MRI brain with and without contrast (or CT brain if MRI not feasible), diagnostic LP with opening pressure, MRI spine if focal peripheral neurological deficits
- Daily 30 min EEG to assess for seizure activity
- Consider anti-IL-6 therapy if associated with CRS

Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

Neurotoxicity Management

Grade 2*

*Continue all supportive care and recommendations from previous grade

- Concurrent CRS: Anti-IL-6 therapy
- No concurrent CRS/refractory: Dexamethasone 10 mg IV q6 hours or methylprednisolone 1 mg/kg IV q12 hours
- Consider transfer to ICU if associated with CRS ≥ grade 2

Grade 3*

*Continue all supportive care and recommendations from previous grade

- ICU transfer
- Corticosteroids per grade 2, continue until improvement to grade 1 then taper
- Management of seizure activity and/or papilledema
- Consider repeat neuroimaging every 2-3 days if consistently ≥ grade 3

Grade 4*

*Continue all supportive care and recommendations from previous grade

- ICU monitoring
- Consider mechanical ventilation
- Continue high-dose corticosteroids until improvement to grade 1 then taper

Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

Elevated Intracranial Pressure

Stage 1 or 2 papilledema with CSF opening pressure <20 mmHg without cerebral edema

- Acetazolamide 1000 mg IV x1 then 250-1000 mg IV every 12 hours (adjust for renal impairment or acid-base balance)

Stage 3, 4, or 5 papilledema with CSF opening pressure >20 mmHg or any sign of cerebral edema

- Methylprednisolone 1 g/day
- Elevate head of bed 30 degrees
- Hyperventilation
- Hyperosmolar therapy: Mannitol or hypertonic saline
- If patient has Ommaya reservoir, drain CSF to target opening pressure <20 mmHg
- Consider neurosurgery consultation and IV anaesthetics
- Daily CT head and metabolic monitoring

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Seizure Management

Prevention

- Levetiracetam 500-750 mg PO BID

Non-convulsive status epilepticus

- Lorazepam 0.5 mg IV and repeat q5 minutes as needed to max 2 mg
- Levetiracetam 500 mg IV bolus, then maintenance
- If persists, add phenobarbital 60 mg IV loading dose

Convulsive status epilepticus

- Lorazepam 2 mg IV and repeat to total of 4 mg
- Levetiracetam 500 mg IV bolus, then maintenance
- If persists, add phenobarbital 15 mg/kg IV loading dose

Maintenance

- Lorazepam 0.5 mg IV q8 hours for 3 doses
- Levetiracetam 1000 mg IV q12 hours
- Phenobarbital 30 mg (non-convulsive) or 1-3 mg/kg (convulsive) IV q12 hours

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Hemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS)

- Group of severe immunological disorders
  - Hyperactivation of macrophages and lymphocytes
  - Proinflammatory cytokine production
  - Lymphohistiocytic tissue inflammation
  - Immune-mediated multiorgan failure
- Clinical features may resemble CRS
- Refractory HLH observed in ~1% of all patients and associated with high mortality
- Diagnostic criteria proposed by Neelapu and colleagues
  - Peak serum ferritin levels >10,000 ng/mL during CRS and any two of the following
    - Grade ≥3 increase in bilirubin, AST, or ALT
    - Grade ≥3 oliguria or increase in serum creatinine
    - Grade ≥3 pulmonary edema
    - Presence of hemophagocytosis in bone marrow or organs

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HLH/MAS Management

Neelapu SS et al. Nat Rev Clin Oncol 2018;15(1):47-62.

Preventative Strategies

- Prevention of infusion related reactions
  - Pre-medicate with acetaminophen and diphenhydramine +/- H2 antagonist 1 hour prior to CAR-T infusion
- Avoid corticosteroids due to known lympholytic effects, except in the following cases:
  - Life-threatening emergency, pre- and post-CAR-T infusion
  - Physiologic replacement in adrenal insufficiency
- Tumor lysis prophylaxis as appropriate
- Antiseizure prophylaxis in patients receiving CAR-Ts known to cause neurotoxicity

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Lymphodepletion

- Tisagenlecleucel
  - B-ALL
    - Fludarabine 30 mg/m^2 days x 4 days
    - Cyclophosphamide 500 mg/m^2 x 2 days
  - DLBCL
    - Fludarabine 25 mg/m^2 x 3 days
    - Cyclophosphamide 250 mg/m^2 x 3 days
    - Alternatively can give bendamustine 90 mg/m^2 x 2 days if unable to receive cyclophosphamide
- Axicabtagene ciloleucel
  - Fludarabine 30 mg/m^2 on days -5, -4, -3
  - Cyclophosphamide 500 mg/m^2 on days -5, -4, -3

Supportive Care and Infection Prophylaxis

	Agent(s)	Start	Discontinue
Antibacterial	Levofloxacin 500 mg PO/IV daily, OR Ciprofloxacin 500 mg PO or 400 mg IV BID	Day 0 if neutropenia expected >1 week	When neutropenia resolves
Antifungal	Fluconazole 200-400 mg PO/IV daily	Day 0 if neutropenia expected >2 weeks	When neutropenia resolves
Antiviral (HSV/VZV)	Valacyclovir 500-100 mg PO daily, OR Acyclovir 400-800 mg PO BID	Day 0	CD4 >200 cells/mcL
PCP prophylaxis	SMX/TMP (preferred) SS PO daily or DS PO MWF, OR Pentamidine, Atovaquone, Dapsone in patients with contraindication or allergy to SMX/TMP	Day +30	CD4 >200 cells/mcL
Hepatitis B prophylaxis	Tenofovir disoproxil fumarate (TdF) 300 mg PO daily, OR Tenofovir alafenamide (TAF) 25 mg PO daily, OR Entecavir 0.5 mg PO daily	Day 0 if HBcAb or HBsAg positive	Day +180-365
Seizure prophylaxis	Levetiracetam 500-750 mg PO/IV BID	Day 0	Day +30

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Risk Evaluation and Mitigation Strategy

- Required for axicabtagene and tisagenlecleucel
- Patients must receive education and patient wallet card
- To become certified to dispense, institutions must:
  - Have at least 2 doses of tocilizumab available on-site for each patient are ready for immediate administration (within 2 hours)
  - Designate an authorized representative to oversee certification and implementation in compliance with REMS program
  - Complete necessary training
  - Establish relevant processes and procedures
  - Enroll in program

Challenges

- Multidisciplinary engagement and training
- Product receipt, storage, labeling of CAR-T cells
- Cost, billing, reimbursement for CAR-T cells
- Variations in grading and management of toxicities
- Anti-IL-6 cost and availability
- Integration with electronic health record, safeguards

Conclusions

- Cellular therapy is expanding in scope and complexity
- Clinical efficacy comes at cost of unique and serious adverse effects
- Management of CRS, ICANS, and HLH/MAS involves timely identification and delivery of supportive care
- Comprehensive infrastructure, including interdisciplinary involvement in clinical processes and procedures, are needed to deliver safe and effective patient care

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