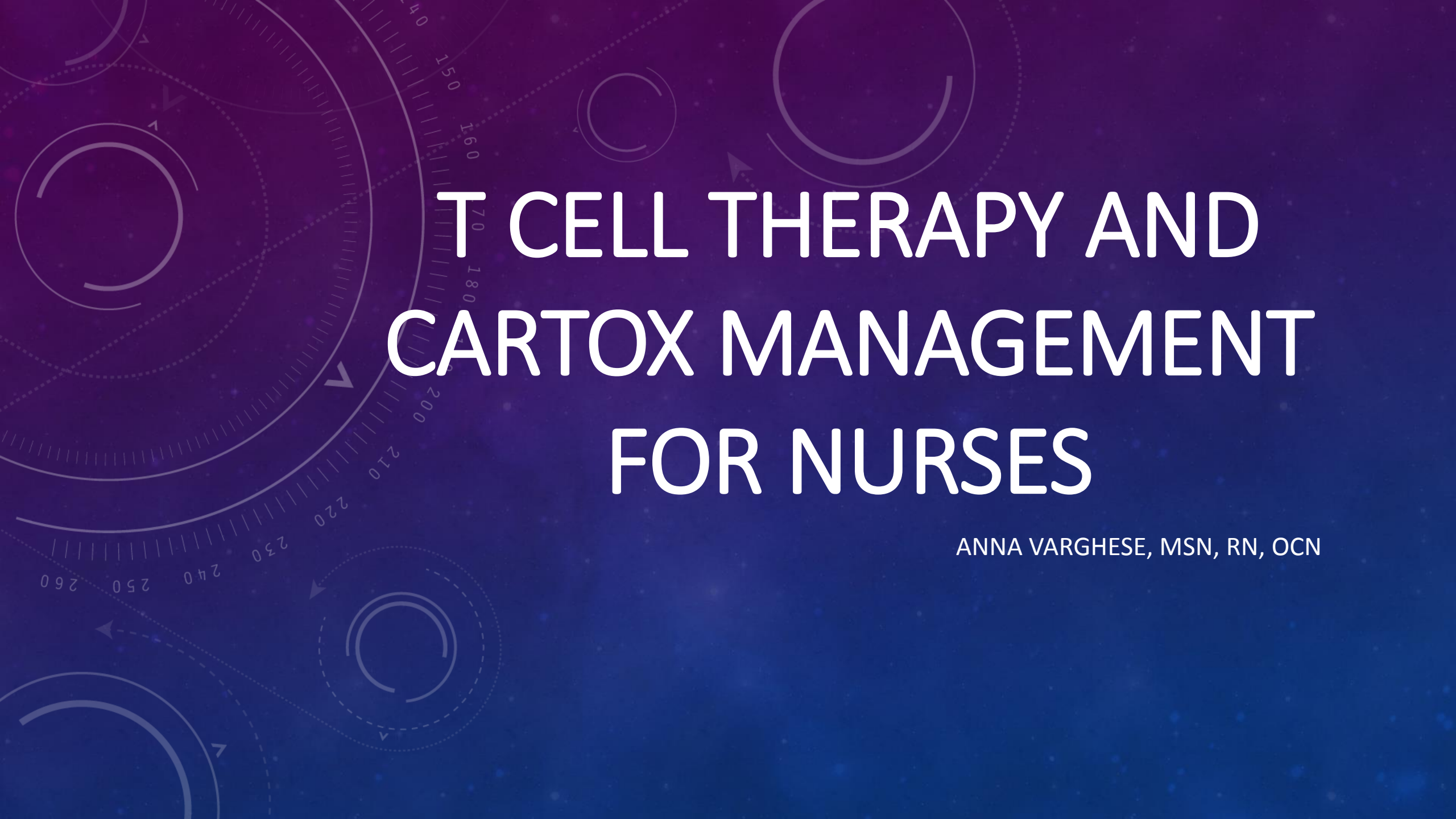


The background is a deep blue gradient with a subtle pattern of white dots. Overlaid on the left side are several concentric circles and a large circular scale with numerical markings from 140 to 260. Some of the circles have dashed lines and arrows, suggesting a circular flow or process.

T CELL THERAPY AND CARTOX MANAGEMENT FOR NURSES

ANNA VARGHESE, MSN, RN, OCN

T CELL THERAPY

What type of T cells are given on G11E?

Who are the patients that are receiving CAR T cells?

What is CAR T cell?

CAR T Cells are Chimeric Antigen Receptors T Cells that are genetically engineered T cells

T CELL THERAPY

Why CAR T cells?

Tumor-specific chimeric antigen receptors (CARs) or TCR gene therapy are a major new technology

More than 50% of patients with refractory hematological and solid tumor malignancies showing durable complete responses to CAR or TCR T-cell therapy

T CELL THERAPY

What does normal T cells do?

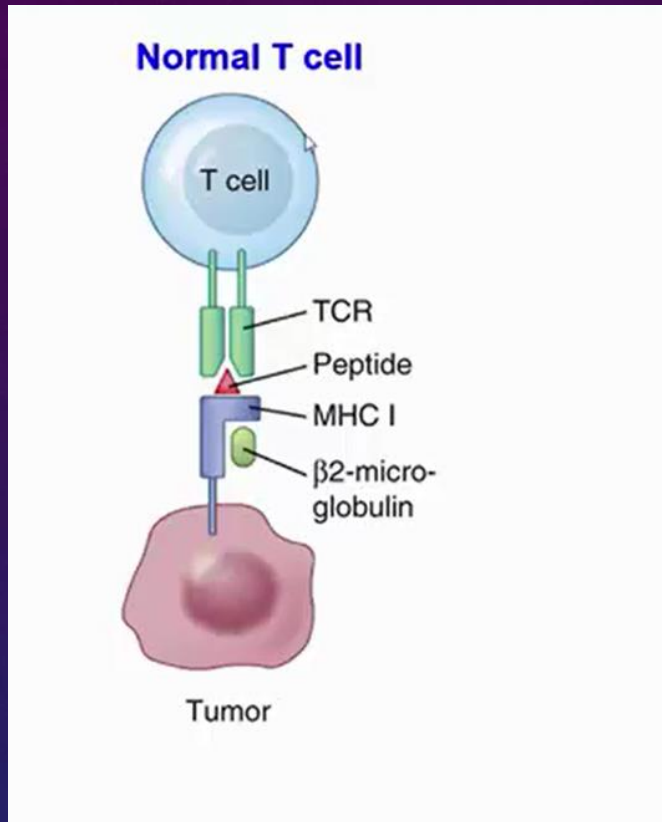
Recognize the pathogenic organisms such as viruses and bacteria

Recognize tumor cells with the help of t cell receptors (TCR)

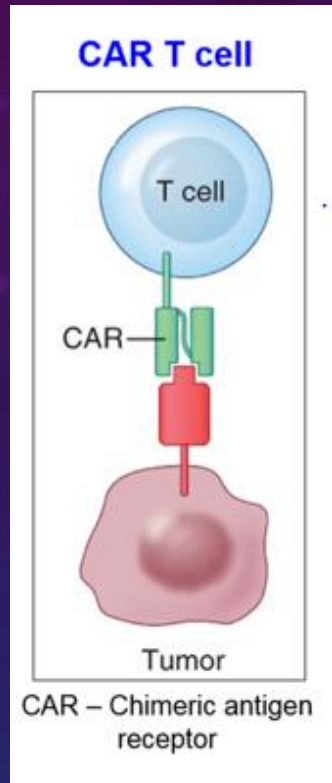
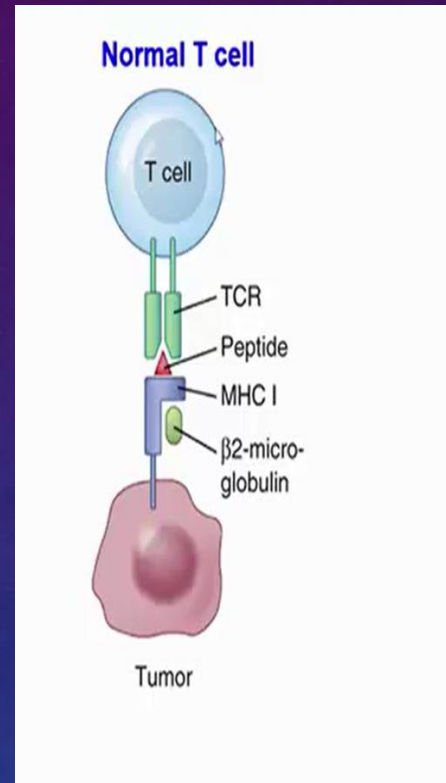
TCR recognize tumor antigens in the forms of peptides (proteins) with the helps of MHC(major histocompatibility complex)

There are more than 25 million copies of T cells in human body

Each T cell has TCR against a unique antigen, whether it is an antigen coming from a virus or bacteria or a tumor cell



T CELL THERAPY



T CELL THERAPY

TIME LINE



Apheresis Product



T cell separation



Cell transfer to bag for growth



Viral transduction



Expand cells

Wash, Concentrate & Freeze



Ready for bedside use

T CELL THERAPY TIME LINE

↑ 2-4 wks manufacturing

**Apheresis /
Blood draw**



Days -5 to -3

Conditioning chemotherapy
Cyclophosphamide
Fludarabine



Day 0

CAR / TCR T cells

- CAR T cells frozen at $\leq -150^{\circ}\text{C}$ in GMP facility until the subject is ready for infusion
- Product thawed at bedside and infused via CVC/PICC/Port-a-cath
- No filter used for infusion
- Subjects hospitalized for infusion of T cells and remain hospitalized for at least 7 days following treatment

- Patient-specific product
- Infused in < 30 mins

T CELL THERAPY

DAY OF INFUSION

- Administer pre-medications as ordered
- NO STEROIDS
- Administer the T cells by RN as a 15 to 30 minute IV infusion via CVC/ PICC/ Port-A-Cath
- Vital signs as ordered

T CELL THERAPY

MAJOR TOXICITIES

Potent therapy, but associated with unique toxicities:

- Cytokine release syndrome (CRS; high fevers, hypotension, hypoxia, multi-organ damage)
- Neurotoxicity (aphasia, encephalopathy, seizures, cerebral edema)
- GVHD

Toxicities can vary

T CELL THERAPY

POTENTIAL REASONS FOR DIFFERENCES IN TOXICITIES

- High vs intermediate / low lympho-depleting chemotherapy
- T cell dose
- CAR / TCR design – antibody clone, hinge region, CD28 vs 4-1BB co-stimulatory domain, TCR affinity, TCR allo-reactivity
- CAR T cell product – Bulk vs T-cell subset separation, duration of culture, stimulation with beads vs antigen-presenting cells
- Clinical parameters – ALL vs NHL vs solid tumors, age, tumor bulk, sites of disease

T CELL THERAPY

CARTOX MANAGEMENT PLAN AT MDA

- PI informs CARTOX Teams at patient admission:
 - PI responsible for daily follow-up, coordination of consulting and management information, and final decisions on care
- All patients will have baseline brain MRI
- CARTOX Neurology Team will perform daily evaluations and EEGs as indicated, oversee neurotoxicity grading, and assist with management of neurologic changes
- CARTOX Intensive Care Team will perform twice-daily evaluations; if significant deterioration in status, will assist primary team in seamless transfer to MICU

T CELL THERAPY

Management

T CELL THERAPY

TOXICITIES

Cytokine Release Syndrome (CRS)
Fever
Neurotoxicity

Macrophage Activation
Syndrome/ HLH
T-cell Infusion Reaction
Tumor Lysis Syndrome
B-cell Aplasia
GVHD
Replication Competent Virus
Uncontrolled T-cell Proliferation
Clonality and Insertion
Oncogenesis

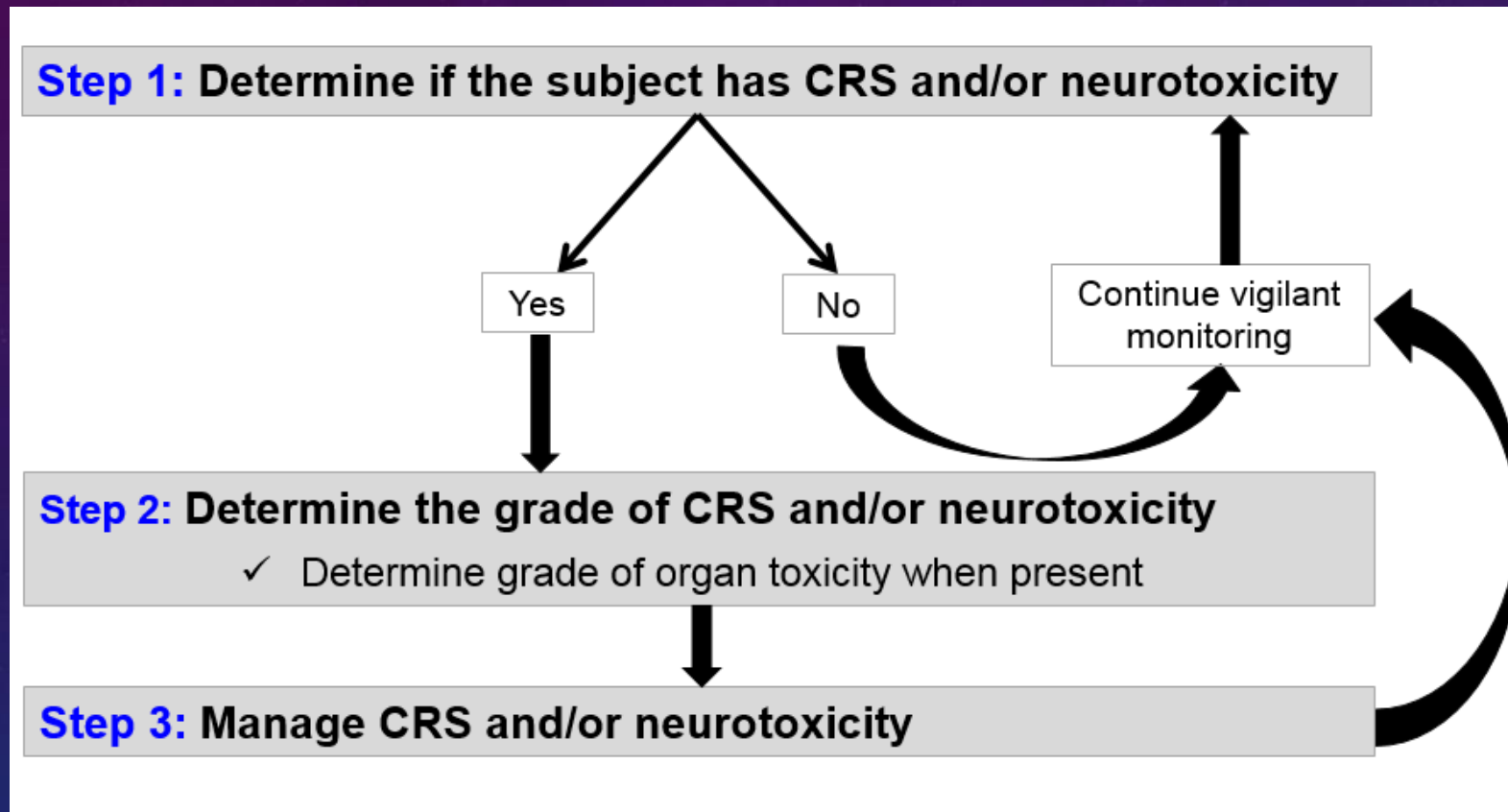


T CELL THERAPY

CYTOKINE RELEASE SYNDROME

T CELL THERAPY

CYTOKINE RELEASE SYNDROME (CRS)



T CELL THERAPY

CRS: FOUNDATION OF MANAGEMENT

Vigilant monitoring for signs of CRS

- From the first CAR T cell infusion through the primary response assessment time point (**28days** after the final CAR T cell infusion)

Supportive Care

- Prompt intervention is essential for patients with early onset of symptoms at Grade 2 and higher
- Prevent the development of severe CRS
- Provide individualized treatment based on the patients' clinical needs

T CELL THERAPY

CRS: SIGNS & SYMPTOMS

- Fever
- Hypoxia
- Hypotension
- Neurologic Changes

Prediction of risk of developing CRS

- Elevated CRP ($\geq 20\text{mg/dl}$)
- Elevated Serum Ferritin ($>5000\text{ng/ml}$)

T CELL THERAPY

CRS GRADING CRITERIA

Table 6: Grading Criteria for CRS

Grade	Description of Symptoms
1 Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgias, malaise)
2 Moderate	Require and respond to moderate intervention: <ul style="list-style-type: none">• Oxygen requirement $< 40\%$, or• Hypotension responsive to fluids or low dose of a single vasopressor, or• Grade 2 organ toxicity (by CTCAE v4.03)
3 Severe	Require and respond to aggressive intervention: <ul style="list-style-type: none">• Oxygen requirement $\geq 40\%$, or• Hypotension requiring high dose of a single vasopressor (e.g., norepinephrine $\geq 20 \mu\text{g}/\text{min}$, dopamine $\geq 10 \mu\text{g}/\text{kg}/\text{min}$, phenylephrine $\geq 200 \mu\text{g}/\text{min}$, or epinephrine $\geq 10 \mu\text{g}/\text{min}$), or• Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to $\geq 20 \mu\text{g}/\text{min}$ norepinephrine), or• Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.03)
4 Life-threatening	Life-threatening: <ul style="list-style-type: none">• Requirement for ventilator support, or• Grade 4 organ toxicity (excluding transaminitis) (by CTCAE v4.03)
5 Fatal	Death

Adapted from (Lee 2014, Lee 2015a)

T CELL THERAPY

HOW DO WE TREAT CRS?

Tocilizumab

- Anti-IL-6 receptor antibody (blocks IL-6 action)
- FDA approved for rheumatoid arthritis
- Dosage: 8 mg/kg (not to exceed 800 mg) IV over 60 mins
- Up to 3 doses of Tocilizumab may be given within a 24-hour period
- Tocilizumab is a part of the admission order set in supportive treatment plan. The admission nurse have to release the order. Once released, it will reside in the PRN medication section in MAR. Once a physician gives you OKAY TO GIVE TOCILIZUMAB, you have to administer it within 15 minutes. CALL PHARMACY right away to deliver the medication
- Call attending physician or PI if there is a delay in administering Tocilizumab

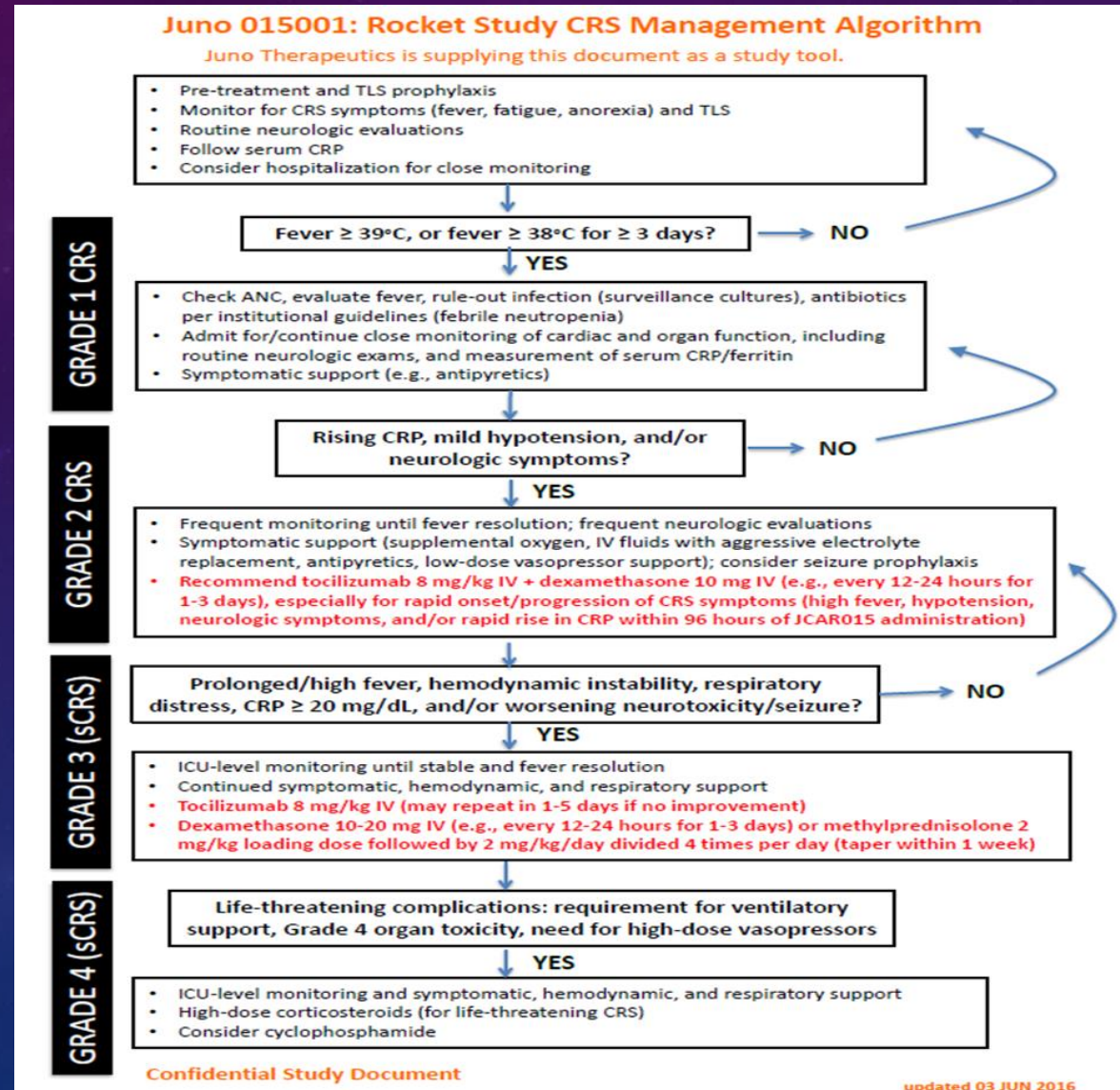
T CELL THERAPY

HOW DO WE TREAT CRS?

- Steroids may be used for management of CRS and neurotoxicity when there is no response to tocilizumab
- Dexamethasone 10-20mg IV every 12-24h for 1-3 days

T CELL THERAPY

CRS MANAGEMENT ALGORITHM



T CELL THERAPY

CRS: MANAGEMENT AT MDA

Step 1 – Determine if the subject has Cytokine Release Syndrome (CRS)

- If the subject has any of the following symptoms or signs within the first 2 weeks of CAR T-cell therapy infusion, the subject may have CRS.
 1. Fever (temperature $\geq 38^{\circ}\text{C}$)
 2. Hypotension (SBP <90)
 3. Hypoxia (O_2 saturation $<90\%$ on room air)
 4. Organ toxicity
 - a. Cardiac – tachycardia, arrhythmias, heart block, low or high ejection fraction
 - b. Respiratory – tachypnea, pleural effusion, pulmonary edema
 - c. Gastrointestinal – Nausea, vomiting, diarrhea
 - d. Hepatic – Increased AST, ALT, or bilirubin
 - e. Renal – Acute kidney injury (increased creatinine), decreased urine output
 - f. Skin – Rash
 - g. Coagulopathy – Disseminated intravascular coagulation (DIC)
 - h. Neurologic – confusion, disorientation, agitation, dysphasia, aphasia, tremor, seizures, motor weakness, incontinence, increased intracranial pressure, papilledema, cerebral edema

T CELL THERAPY

CRS GRADING

Step 2 – Determine the grade of CRS

- CRS grade should be determined at least twice daily and any time there is a change in patient's status.

Category	Symptom/Sign	CRS Grade 1 ^a	CRS Grade 2 ^b	CRS Grade 3 ^b	CRS Grade 4 ^b
Vital signs	Temp $\geq 38^{\circ}\text{C}$	Yes	Any	Any	Any
	SBP < 90	No	Responds to IV fluids or low-dose vasopressor	Needs high-dose or multiple vasopressors ^d	Life- threatening
	Needing oxygen for O_2 sat >90%	No	FiO2 <40%	FiO2 $\geq 40\%$	Needing ventilator support
Organ toxicity ^c	See Step 1	Grade 1	Grade 2	Grade 3 or grade 4 transaminitis	Grade 4 except grade 4 transaminitis

^a Grade 1 CRS may manifest as fever and/or grade 1 organ toxicity

^b For Grades 2, 3, or 4 CRS, any one of the criteria other than temperature is sufficient

^c See [Appendix 1](#) and CTCAE, version 4 for grading of organ toxicity.

^d See [Appendix 2](#) for definition of high-dose vasopressors

T CELL THERAPY

CRS MANAGEMENT

Step 3 – Manage CRS and organ toxicity

* High risk for severe CRS: Bulky disease, co-morbidities, age ≥ 60 yrs, early onset CRS (<3 days)

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or grade 1 organ toxicity	<ul style="list-style-type: none"> Acetaminophen and hypothermia blanket as needed for fever Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic Assess for infection with blood and urine cultures, and chest x-ray Consider antibiotics and <u>filgrastim</u> if <u>neutropenic</u> IV fluids as needed Symptomatic management of constitutional symptoms and organ toxicities
Grade 2	Hypotension	<ul style="list-style-type: none"> IV fluid bolus of 500 – 1000 mL normal saline Tocilizumab 8 mg/kg IV q 6h as needed for up to 3 doses / 24h May give a second IV fluid bolus if SBP remains <90 in 1 hour If hypotension persists after two fluid boluses, start vasopressors, transfer patient to ICU, and obtain ECHO In patients at high-risk* or if hypotension persists after 1-2 doses of tocilizumab, may use Dexamethasone 10 mg IV q 6h Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	<ul style="list-style-type: none"> Use supplemental oxygen as needed Use tocilizumab +/- corticosteroids as in hypotension Manage fever and constitutional symptoms as in Grade 1 CRS
	Grade 2 organ toxicity	<ul style="list-style-type: none"> Manage organ toxicity as per standard guidelines Use tocilizumab +/- corticosteroids as in hypotension Manage fever and constitutional symptoms as in Grade 1 CRS

T CELL THERAPY

CRS MANAGEMENT

Step 3 – Manage CRS and organ toxicity

CRS Grade	Symptom or Sign	Management
Grade 3	Hypotension	<ul style="list-style-type: none"> • IV fluid boluses as needed as in Grade 2 CRS • Tocilizumab 8 mg/kg IV q 6h as needed for up to 3 doses / 24h if not administered previously • Use vasopressors as needed • Transfer patient to ICU and obtain ECHO if not done already • Start Dexamethasone 10 mg IV q 6h* • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	<ul style="list-style-type: none"> • Use supplemental oxygen as needed • Use tocilizumab + corticosteroids as above • Manage fever and constitutional symptoms as in Grade 1 CRS
	Grade 3 organ toxicity or grade 4 transaminitis	<ul style="list-style-type: none"> • Manage organ toxicity as per standard guidelines • Use tocilizumab + corticosteroids as above • Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 4	Hypotension	<ul style="list-style-type: none"> • Manage as in Grade 3 CRS
	Hypoxia	<ul style="list-style-type: none"> • Mechanical ventilation
	Grade 4 organ toxicity excluding transaminitis	<ul style="list-style-type: none"> • Manage as in Grade 3 CRS

*Methylprednisolone has also been used at doses ranging from 1 mg/kg IV q12 h or 500 mg IV q12 h for 3 days followed by rapid taper at 250 mg q12 h x 2 days, 125 mg q12h x 2 days, and 60 mg q12 h x 2 days). Steroid taper may be individualized depending on toxicity

T CELL THERAPY

CTCAE GRADING OF COMMON ORGAN TOXICITIES

Category	Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac	Sinus tachycardia	Asymptomatic, No intervention needed	Symptomatic, non-urgent intervention indicated	Urgent intervention indicated	-
	Arrhythmia or Heart block	Asymptomatic, No intervention needed	Symptomatic, non-urgent intervention indicated	Urgent intervention indicated	Life-threatening
	Ejection fraction decreased	-	EF 50-40% or 10-19% drop from baseline	EF 39-20% or >20% drop from baseline	EF <20%
Respiratory	Pleural effusion	Asymptomatic, No intervention needed	Symptomatic, intervention indicated (diuretics or thoracentesis)	Symptomatic with respiratory distress; needs surgical intervention (chest tube or pleurodesis)	
	Pulmonary edema	Minimal dyspnea on exertion	Moderate dyspnea one exertion; Medical intervention indicated; limits instrumental ADL	Dyspnea at rest; oxygen indicated; limits self-care ADL	Life-threatening; urgent intervention or ventilatory support indicated
*For toxicities not listed here, please refer to CTCAE, version 4 for grading.					

T CELL THERAPY

CTCAE GRADING OF COMMON ORGAN TOXICITIES

Category	Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without dehydration or weight loss	Inadequate oral caloric or fluid intake, tube feeding or TPN	-
	Vomiting	1-2 episodes / 24 hrs	3-5 episodes / 24 hrs	>6 episodes / 24 hrs, tube feeding or TPN	Life-threatening
	Diarrhea	Increase of <4 stools/day over baseline	Increase of 4-6 stools/day over baseline	Increase of ≥7 stools/day over baseline; limits self-care ADL	Life-threatening
Hepatic	AST or ALT	>ULN – 3 x ULN	>3-5 x ULN	>5-20 x ULN	>20 x ULN
	Total Bilirubin	>ULN – 1.5 x ULN	>1.5-3 x ULN	>3-10 x ULN	>10 x ULN
Renal	Urine output decreased	-	-	Oliguria (<80 mL / 8 hrs)	Anuria (<240 mL / 24 hrs)
	Acute kidney injury	Creatinine 1.5-2 x above baseline	Creatinine 2-3 x above baseline	Creatinine >3 x baseline or > 4 mg/dL	Life-threatening; dialysis indicated
Coagulopathy	DIC	-	Laboratory findings with no bleeding	Laboratory findings with bleeding	Life-threatening; Urgent intervention indicated

*For toxicities not listed here, please refer to CTCAE, version 4 for grading. **ULN** = Upper Limit of Normal



T CELL THERAPY

FEVER

T CELL THERAPY

FEVER: MANAGEMENT

- Evaluate for infection
- Treat with antibiotics & fluids
- Supportive care per institutional policies & procedures
- Management of neutropenic fever as indicated



T CELL THERAPY

NEUROTOXICITY

CAR T CELL THERAPY

NEUROTOXICITY

Step 1: Determine if the subject has CRS and/or neurotoxicity

Yes

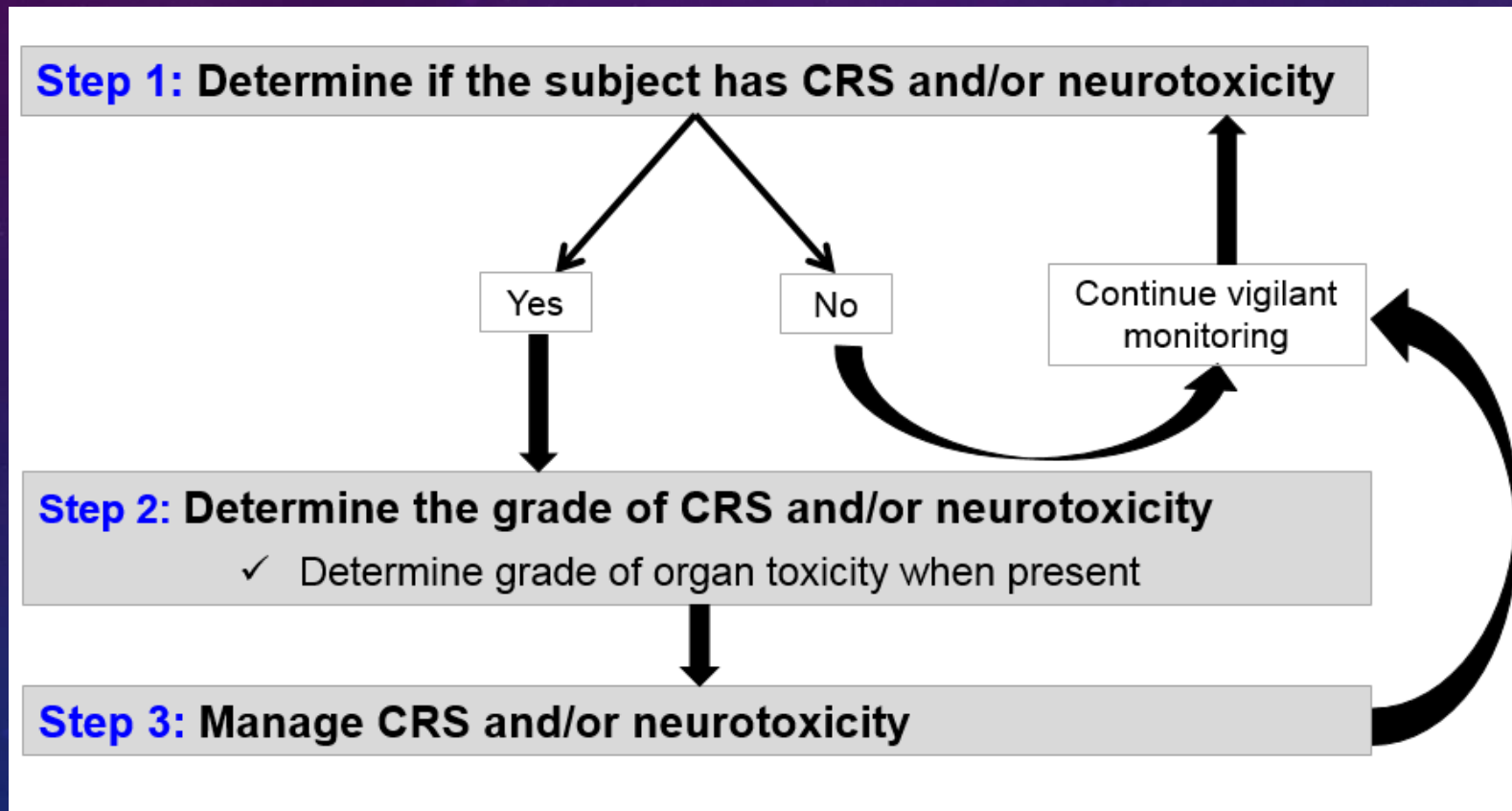
No

Continue vigilant
monitoring

Step 2: Determine the grade of CRS and/or neurotoxicity

✓ Determine grade of organ toxicity when present

Step 3: Manage CRS and/or neurotoxicity



T CELL THERAPY

NEUROTOXICITY

- Can occur with or without CRS
- May be the earliest symptom of sCRS
- Begins 5 to 7 days post infusion of CAR T cells
- Can be reversible
- The duration of neurological changes can occur up to 42 days

Symptoms

- Confusion
- Delirium
- Expressive aphasia
- Obtundation
- Myoclonus seizure like/
seizure activity

T CELL THERAPY NEUROTOXICITY

- Exact etiology remains unclear
- No clear evidence of expression of CD19 in CNS
- Possibility of CNS occult disease
- MRI of brain is usually negative
- CSF usually positive for CAR T cells
- EEG-non focal or non-convulsive seizure pattern
- Observed with both CD19 and non-CD19 CAR T cell therapies

T CELL THERAPY

NEUROTOXICITY MANAGEMENT

- Monitor closely for the signs and symptoms, especially with early onset (within 96 hours of infusion)
- Administer Tocilizumab and corticosteroids
- Neurological assessment
- Use of Keppra for selected patients

T CELL THERAPY NEUROTOXICITY

- Onset of neurotoxicity symptoms may be biphasic
 - 1st phase (Days 0-5) – symptoms may appear with other CRS symptoms
 - 2nd phase (After day 5) – starts after CRS symptoms have subsided
 - Neurotoxicity such as seizures may occur as late as 3rd or 4th week after CAR T cell therapy
- Neurotoxicity typically lasts 2-4 days but may vary in duration from few hours to few weeks. It is generally reversible.
- Tocilizumab might reverse neurological toxicity during the 1st phase but not the 2nd phase
- Corticosteroids may be used to manage neurotoxicity if tocilizumab is not effective
- Seizure prophylaxis is recommended with levetiracetam (Keppra 500 or 750 mg oral/IV q 12 hrs) from day 0

T CELL THERAPY

NEUROTOXICITY

Step 2 – Determine the CTCAE and MDACC grade of neurotoxicity

CTCAE	Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
	Level of consciousness	Mild drowsiness / sleepiness	Moderate somnolence, limiting instrumental ADL	<u>Obtundation</u> or stupor	Life-threatening needing urgent intervention or mechanical ventilation
	Orientation / Confusion	Mild disorientation / confusion	Moderate disorientation, limiting instrumental ADL	Severe disorientation, limiting self-care ADL	
	ADL / Encephalopathy	Mild limiting of ADL	Limiting instrumental ADL	Limiting self-care ADL	
	Speech	Dysphasia not impairing ability to communicate	Dysphasia with moderate impairment in ability to communicate spontaneously	Severe receptive or expressive dysphasia, impairing ability to read, write or communicate intelligibly	-
	Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures
	Incontinent or motor weakness			Bowel / bladder incontinence; Weakness limiting self-care ADL, disabling	
	MDACC 10-point Neurotoxicity grade	Mild (7-9)	Moderate (3-6),	Severe (1-2), grade 1 and 2 papilledema with CSF opening pressure (op) < 20 mm Hg	Critical (Obtunded; convulsive status epilepticus; motor weakness, grade 3, 4 & 5 papilledema, CSF op ≥ 20 mm Hg, cerebral edema)

T CELL THERAPY

NEUROTOXICITY

Representative subject: Impaired handwriting could be an early sign of neurotoxicity

Day 4
9 am

I love Shawnee, KS.

MMSE score
29/30

Day 5
01:30 PM

Toci 8 mg/kg

Shawnee is a ~~great~~ ^{beautiful} ~~area~~ ^{area}

27/30

Day 5
03:30 PM

I'm ~~sure~~ ^{sure} ~~about~~ ^{about}

27/30

Day 6
9 am

I miss my kids.

29/30

T CELL THERAPY NEUROTOXICITY

Step 3 – Manage neurotoxicity

Grade	Management
Grade 1	<ul style="list-style-type: none"> • Vigilant supportive care; Aspiration precautions • Daily simplified neurologic examination as in Appendix 3 • Fundus exam to document +/- papilledema • MRI brain and diagnostic lumbar puncture with opening pressure (op); MRI spine if focal signs • Daily 30 min EEG; if no seizures on EEG, continue levetiracetam 750 mg q 12 h • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Appendix 4 • Consider <u>Tocilizumab</u> 8 mg/kg IV if associated with Grade 2 or greater CRS
Grade 2	<ul style="list-style-type: none"> • Manage as per Grade 1 • Consider ICU transfer if associated with Grade 2 or greater CRS • <u>Tocilizumab</u> 8 mg/kg IV if associated with Grade 2 or greater CRS
Grade 3	<ul style="list-style-type: none"> • Manage as per Grade 1 • Tocilizumab 8 mg/kg IV q 6h for up to 3 doses / 24 h if not administered previously • Consider corticosteroids (e.g. dexamethasone 10mg IV q6h or methylprednisolone 1 mg/kg IV q 12h) for worsening symptoms despite tocilizumab; Continue steroids until reversal of toxicity and taper over 2 weeks • Low grade (1 & 2) papilledema with CSF op < 20 mm Hg, see Appendix 6 • Consider ICU transfer if associated with Grade 2 or greater CRS • Consider repeat neuro-imaging (CT or MRI) q 2-3 days if persistent neurotoxicity ≥ grade 3
Grade 4	<ul style="list-style-type: none"> • Manage as per Grade 3 • ICU monitoring • High-dose corticosteroids (e.g. Methylprednisolone IV 1 g/day x 3 days followed by rapid taper at 250 mg q12 h x 2 days, 125 mg q12 h x 2 days, and 60 mg q12 h x 2 days); Continue until reversal of toxicity and taper over 2 weeks • For convulsive status epilepticus, treat as per algorithm in Appendix 5 • High grade (3, 4, & 5) papilledema, CSF op ≥ 20 mm Hg, or cerebral edema, see Appendix 6

T CELL THERAPY

Management of non-convulsive status epilepticus

- Assess ABC/airway positioning/high flow O₂, check blood sugar
- Ativan 0.5 mg IV × 1 with additional 0.5 mg IV q 5 min up to a total of 2 mg to control electrographical seizures
- Levetiracetam 500 mg IV bolus
- If seizures persist, transfer to ICU and add a second agent Phenobarbital loading dose 60 mg IV
- Maintenance doses after resolution of status epilepticus
 - ✓ Ativan 0.5 mg IV q 8 hours × 3 doses
 - ✓ Increase Keppra to 1000 mg IV q 12 h
 - ✓ Phenobarbital 30 mg IV q 12 h

T CELL THERAPY

Management of convulsive status epilepticus

- Assess ABC/airway positioning / high flow O₂, check blood sugar
- MERIT team to evaluate for transfer to ICU
- Ativan 2 mg IV × 1 with additional 2 mg IV to a total of 4 mg to control electrographic seizures
- **Levetiracetam** 500 mg IV bolus
- If seizures persist, transfer to ICU and add a second agent Phenobarbital loading dose 15 mg/kg IV
- Maintenance doses after resolution of status epilepticus
 - ✓ Ativan 0.5 mg IV q 8 h × 3 doses
 - ✓ Increase **Levetiracetam** to 1000 mg IV q 12 h
 - ✓ Phenobarbital 1-3 mg/kg IV q 12 h
 - ✓ Continuous EEG, if seizures are refractory

T CELL THERAPY

MANAGEMENT OF CEREBRAL EDEMA

- **Grade 1 and 2 papilledema with CSF op < 20 mm Hg without cerebral edema**
 - ✓ Acetazolamide (Diamox) 1000 mg IV followed by 250 mg-1000 mg iv q 12 h (adjust dose based on renal and acid/base balance)
- **Grade 3, 4, and 5 papilledema, any cerebral edema on imaging studies, or CSF op ≥ 20 mm Hg**
 - ✓ Use high-dose steroids as per Grade 4 neurotoxicity along with the following measures for management of cerebral edema
 - ✓ Elevate head to 30 degrees
 - ✓ Hyperventilation to achieve target PaCO₂ of 28-30 mm Hg for 24 h
 - ✓ Hyperosmolar therapy with either mannitol 20% **or** hypertonic saline (3% or 23.4%)
 - Mannitol: initial dose 0.5-1 g/kg, maintenance at 0.25-1 g/kg every 6 h (metabolic profile and serum osmolality q 6 h, hold mannitol if serum osmolality ≥ 320 mOsm/kg or osmolol gap ≥40)
 - Hypertonic saline: initial 250 mL of 3% hypertonic saline, maintenance at 50-100 mL/h (q 4 h electrolytes, hold infusion if serum Na ≥155 mEq/L)
 - Imminent herniation: Initial 30 mL of 23.4% hypertonic saline (may repeat in 15 min)
 - ✓ If patient has ommaya reservoir, drain CSF to target op < 20 mm Hg
 - ✓ Consider neurosurgery consultation, IV anesthetics for burst-suppression EEG
 - ✓ Metabolic profile q 6 h, daily Head CT and adjust above medications to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia and hypotension.

T CELL THERAPY

SUPPORTIVE CARE CONSIDERATIONS

- Consult to neurology on or before day of T-cell infusion
- Seizure prophylaxis (when permitted by protocol)
 - ✓ Levetiracetam 500 – 750 mg PO Q12h
- CRP and Ferritin daily starting on cell infusion day
- Patients with high tumor burden or risk for tumor lysis
 - ✓ Allopurinol or rasburicase (if criteria met)
- Hydration: NS at 63 ml/hr if patient can tolerate
- Telemetry daily starting on day of cell infusion
- Daily weights, vitals signs Q4h, and strict I/O
- PRN medications
 - ✓ Acetaminophen (1st choice) or Ibuprofen (2nd choice) for fever $> 38.3^{\circ}\text{C}$
 - ✓ Medi-Therm Cooling blanket prn fever $> 38.3^{\circ}\text{C}$
 - ✓ NS 500 to 1000 ml bolus prn SBP < 90 mmHg
 - ✓ PRN tocilizumab order (for TID prn). Nurse needs to call pharmacy to make when it is needed

T CELL THERAPY

One Connect Documentation & Order sets

T CELL THERAPY

Order Sets

CARTOX – Cytokine Release order set

General (no defaults and keep all options viewable):

- ☐ Vital Signs – Routine, Q2h
- ☐ Strict intake and output – Routine, every 8 hours
- ☐ Titrate oxygen to SPo2 greater than – Routine; SPO2 greater than 93
- ☐ Nasal cannula oxygen – Routine, Continuous; Rate in liters per minute: 2L/M
- ☐ Blood Culture, peripheral – STAT for 1 occurrence
- ☐ Blood culture, central – STAT for 1 occurrence
- ☐ X-ray Chest 1 view – STAT, 1 time imaging for 1 occurrence
- ☐ X-ray chest 2 view – STAT, 1 time imaging for 1 occurrence
- ☐ EKG, 12-Lead (portable) – STAT, once for 1 occurrence

Consults (no defaults and keep all options viewable):

- ☐ Infectious Disease
- ☐ Neurology
- ☐ Cardiology
- ☐ Nephrology

Medications (no defaults and keep all options viewable):

- ☐ "OK to give" order for tocilizumab (doing this b/c tocilizumab lives as a prn order on the MAR) (order # BCN1045)
- ☐ Acetaminophen 650 mg po q6h prn temp ≥ 38.5 x 48 hrs
- ☐ Acetaminophen (Ofirmev) 650 mg IV Q6h prn temp ≥ 38.5 X 48 hrs
- ☐ ____ mL NS IV bolus x 1 dose – once, STAT (no default) (order # 40800000205)
- ☐ Apply cooling blanket – Routine, Until discontinued
- ☐ Dexamethasone 10 mg IV – Once, STAT (this is default, keep other frequencies as an option)
- ☐ Methylprednisolone 1 gram IV – once, STAT --followed by--
- ☐ Methylprednisolone 250 mg IV q6h x 8 doses --followed by--
- ☐ Methylprednisolone 250 mg IV Q12h x 4 doses --followed by--
- ☐ Methylprednisolone 125 mg IV Q12h x 4 doses --followed by--
- ☐ Methylprednisolone 60 mg IV q12h x 4 doses --followed by--

T CELL THERAPY

NEUROTOXICITY ORDER SET

Consults

- ☐ Neurology
- ☐ Neurosurgery
- ☐ Ophthalmology

IP CARTOX - Neurotoxicity [3041200125]	
Labs	
Chemistry Basic	
☐ Comprehensive Metabolic Panel	Every 6 hours
☐ Osmolality	Every 6 hours
☐ Electrolyte Panel	Every 4 hours
General	
General	
☐ Aspiration precautions	Routine, Continuous
☐ Neuro/vascular checks	Routine, Daily (Scheduled) Neuro/vascular checks include orientation to year, month, day, hospital, president. Have patient write a standard sentence (e.g. National bird is the bald eagle). Name 3 objects (point to clock, pen, button). Count backwards from 100.
☐ MRI Brain with and without Contrast	STAT, 1 time Imaging For 1 Occurrences Reason for Exam: Is the patient pregnant? What is the patient's sedation requirement? Does the patient have a pacemaker or a defibrillator? Does the patient have aneurysm clips? Does the patient have tissue expanders? Is the patient over 350 lbs?
☐ MRI Brain without Contrast	STAT, 1 time Imaging For 1 Occurrences Reason for Exam: Is the patient pregnant? What is the patient's sedation requirement? Does the patient have a pacemaker or a defibrillator? Does the patient have aneurysm clips? Does the patient have tissue expanders? Is the patient over 350 lbs?
☐ MRI Cervical, Thoracic and Lumbar Spine w and wo Contrast	STAT, 1 time Imaging For 1 Occurrences Reason for Exam: Is the patient pregnant? What is the patient's sedation requirement? Does the patient have a pacemaker or a defibrillator? Does the patient have aneurysm clips? Does the patient have tissue expanders? Is the patient over 350 lbs?
☐ MRI Cervical, Thoracic and Lumbar Spine without Contrast	STAT, 1 time Imaging For 1 Occurrences Reason for Exam: Is the patient pregnant? What is the patient's sedation requirement? Does the patient have a pacemaker or a defibrillator? Does the patient have aneurysm clips? Does the patient have tissue expanders? Is the patient over 350 lbs?
☐ EEG	STAT, Once Reason for Exam: Is patient on blood thinners?
☐ Head of Bed	Routine, Until discontinued, Starting today Degrees: 30

T CELL THERAPY

NEUROTOXICITY ORDER SET

Acetazolamide for grade 1 or 2
Papilledema with CSF Opening
Pressure less than 20 mmHg
without cerebral edema

Mannitol and sodium chloride 3%
Grade 3, 4, and 5 papilledema,
any cerebral edema on imaging
studies, or CSF Opening pressure
greater than
or equal to 20 mmHg

Medications	
Neurotoxicity Medications:	
☐ OK to give Tocilizumab	Details
☒ LORazepam (ATIVAN) IV	intravenous Once, For 1 Doses
☐ levetIRAcetam (KEPPRA) IVPB	500 mg, intravenous Once, For 1 Doses
☐ For Non-Convulsive seizure: PHENobarbital (LUMINAL) IVPB	60 mg, for 20 Minutes, intravenous Once, For 1 Doses
☐ For convulsive seizure: Phenobarbital Panel:	"Followed by" Linked Panel
☐ PHENobarbital (LUMINAL) IVPB bolus	15 mg/kg, intravenous Once, For 1 Doses
☐ PHENobarbital (LUMINAL) IVPB bolus	1 mg/kg, intravenous Every 12 hours Dose is 1 to 3 mg/kg Q12H
☐ dexamethasone (DECADRON) IV	10 mg, intravenous Every 6 hours
☐ Methylprednisolone Panel:	"Followed by" Linked Panel
☐ methylIPREDNISolone sodium succinate (Solu-MEDROL) IV	1,000 mg, intravenous Once, For 1 Doses
☐ methylIPREDNISolone sodium succinate (Solu-MEDROL) IV	250 mg, intravenous Every 6 hours scheduled, For 8 Doses
☐ methylIPREDNISolone sodium succinate (Solu-MEDROL) IV	250 mg, intravenous Every 12 hours, For 4 Doses
☐ methylIPREDNISolone sodium succinate (Solu-MEDROL) IV	125 mg, intravenous Every 12 hours, For 4 Doses
☐ methylIPREDNISolone sodium succinate (Solu-MEDROL) IV	60 mg, intravenous Every 12 hours, For 4 Doses
☐ For cerebral edema: Acetazolamide Panel:	"Followed by" Linked Panel
☐ acetaZOLAMIDE (DIAMOX) IV	1,000 mg, intravenous, For 1 Doses
☐ acetaZOLAMIDE (DIAMOX) IV	250 mg, intravenous Every 12 hours
☐ For cerebral edema: Mannitol + Labs Panel:	"Followed by" Linked Panel
☐ mannitol (OSMITROL) IVPB	0.5 g/kg, intravenous, For 1 Doses Hold mannitol if serum osmolality greater than or equal to 320 mOsm/kg or osmol gap greater than or equal to 40.
☐ mannitol (OSMITROL) IVPB	0.25 g/kg, intravenous Every 12 hours Hold mannitol if serum osmolality greater than or equal to 320 mOsm/kg or osmol gap greater than or equal to 40.
☐ For cerebral edema: Sodium Chloride Panel:	"Followed by" Linked Panel
☐ sodium chloride 3% (HYPERTONIC) IV	250 mL, intravenous, For 1 Doses Hold infusion if serum sodium greater than or equal to 155 mEq/L.
☐ sodium chloride 3% (HYPERTONIC) IV	50 mL/hr, intravenous Hold infusion if serum sodium greater than or equal to 155 mEq/L.

T CELL THERAPY

CARTOX FLOWSHEET

CRS Syndrome	
Temp	
BP	
SpO2	
FiO2 (%)	
SP02/Fi02 (Calculated)	
 Cardiac	
 Respiratory	
 Gastrointestinal	
 Hepatic	
 Renal	
 Coagulopathy	
CRS Syndrome Grade	
Neurotoxicity	
Level of Consciousness	
ADL / Encephalopathy	
Speech	
Seizure	
Incontinent or motor weakness	
Orientation	
Ability to Write	
Name 3 Objects	
Count 10 Backwards	
MDACC Neuro Scale Score	
Neurotoxicity Grade Final	
Physician Notified	
Physician Notified	

T CELL THERAPY

INSTITUTIONAL SUPPORT

CAR T CELL THERAPY

ENHANCING PATIENT SAFETY: CARTOX COMMITTEE

- Established CAR Therapy Toxicity (CARTOX) Committee in March 2016, co-chaired by EJ Shpall and P Hwu
- Includes investigators/providers with expertise in SCT, cellular therapy, hematologic cancers, solid tumors, immunology, IMT, neurology, pharmacy, ICU, nursing, research administration, and EHR
- Formed designated CARTOX teams representing ICU, neurology, pharmacy, and EHR
- Developed comprehensive CAR patient management plan for institutional implementation

T CELL THERAPY

ENHANCING PATIENT SAFETY: CARTOX COMMITTEE

- **Required**: Comprehensive training of all floor nurses, mid-level practitioners, pharmacy staff, and physicians managing CAR patients:
 - Lecturers, slide sets and sign-in sheet provided
 - Reviews CARTOX diagnosis and management algorithms
 - Webinar in development for Education Center (Sept 2016)
- **Required**: Patients to be treated only in designated clinical units, with sufficient telemetry beds:
 - Care to be provided by CARTOX-trained personnel experienced in managing these complicated patients

T CELL THERAPY

ENHANCING PATIENT SAFETY: CARTOX COMMITTEE

- PIs to inform CARTOX Teams at patient admission:
 - PI responsible for daily follow-up, coordination of consulting and management information, and final decisions on care
- All patients will have baseline brain MRI
- CARTOX Neurology Team will perform daily evaluations and EEGs as indicated, oversee neurotoxicity grading, and assist with management of neurologic changes
- CARTOX Intensive Care Team will perform twice-daily evaluations; if significant deterioration in status, will assist primary team in seamless transfer to MICU

T CELL THERAPY

ENHANCING PATIENT SAFETY: CARTOX COMMITTEE

- CARTOX Pharmacy Team will ensure availability of critical CRS-supportive care agents (eg, tocilizumab) for at least 6 patients at all times
- CARTOX Epic Electronic Medical Record *and* Pharmacy Teams will ensure availability of standard admission and supportive care orders for each patient
- CARTOX Epic Electronic Medical Record Team will provide CRS and Neurotoxicity grading systems within EHR:
 - RNs and MDs can assign toxicities and automatically calculate CRS or neurotoxicity grade

T CELL THERAPY

REFERENCES

- CARTOX Management Plan: Overview (original powerpoint created by Elizabeth J. Shpall, MD, Sattva Neelapu, MD, Monica Loghin, MD, Joaquin Buitrago Nurse Educator, Alison Gulbis PharmD)
- JCAR015: Phase 2 study in adult relapsed/ refractory acute lymphoblastic leukemia. (Original power point created by Nikolaus Trede, Senior Medical director, Juno Therapeutics, Inc.)