Example Clinician Educational Material for Providers of Immune Effector Cellular Therapy

Disclaimer: This example is just one of many potential examples of clinician education material that can be provided by a given institution to medical and nursing providers involved in administering and caring for patients receiving immune effector cellular therapy.

The general expectation is that the immune effector cell (IEC) program has clinician-oriented materials, a training program, and documentation of training of key providers of IEC products. This education would address, for example, identification of patients at risk, evaluation of appropriate symptoms, initial management response, workflows for appropriate communication between teams and escalation of care, and access to specialized medications and clinical teams for treatment of severe toxicities. If this example is used, the program is responsible for updating it as new information becomes available.

Clinician Management Plan

- PIs to inform XXXX 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
- Neurology Team will perform daily evaluations and EEGs as indicated, oversee neurotoxicity grading, and assist with management of neurologic changes
- Intensive Care Team will perform at least daily evaluations; if significant deterioration in status, will assist primary team in seamless transfer to MICU

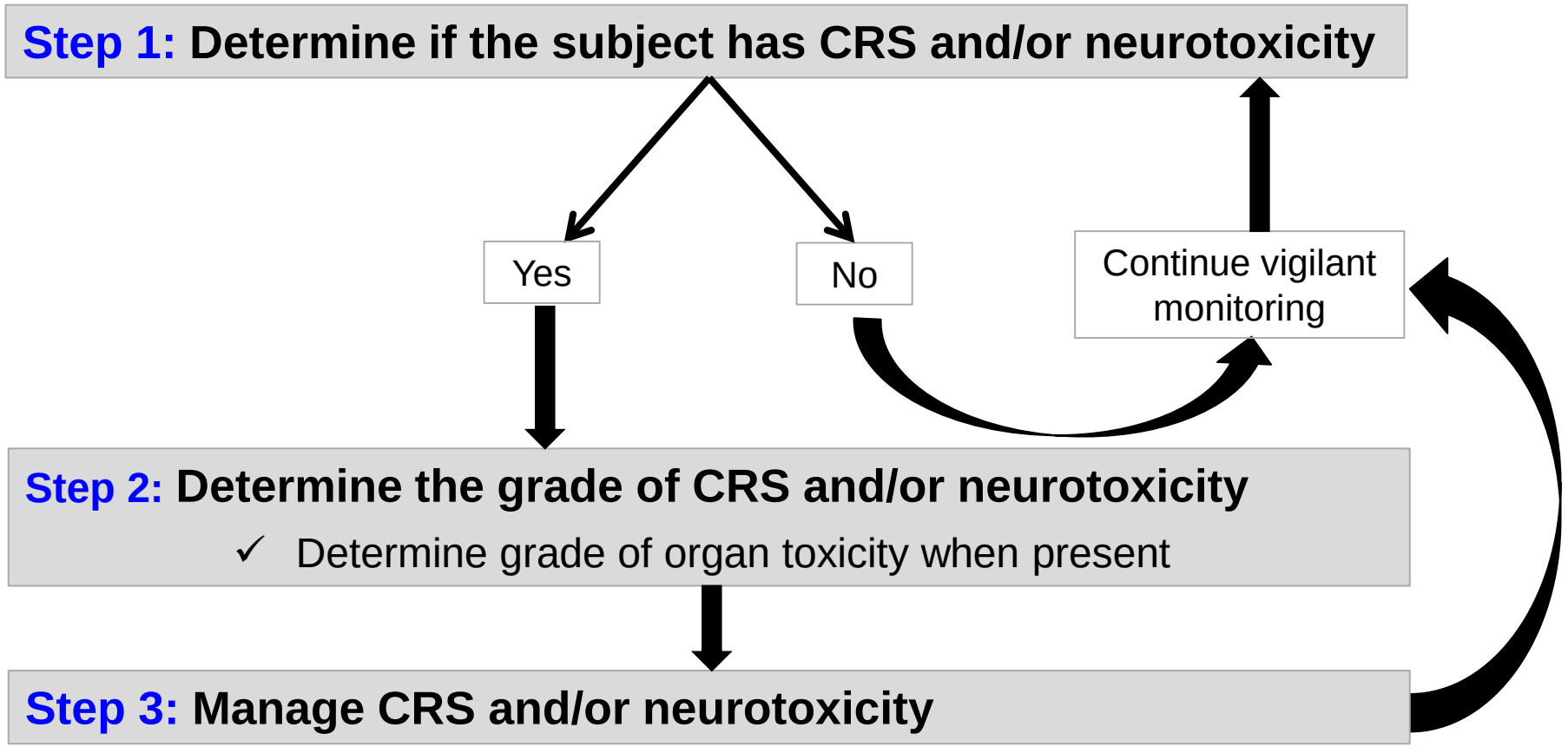
Support Team Management Plan

- Pharmacy Team will ensure availability of critical CRS-supportive care agents (eg, tocilizumab) for at least 6 patients at all times

- Electronic Medical Record *and* Pharmacy Teams will ensure availability of standard admission and supportive care orders for each patient

- 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

CAR T-Cell Therapy Toxicity Assessment and Management



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 ≥ 38^0C)
2. Hypotension (SBP <90)
3. Hypoxia (O2 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

Adapted from Lee et al, Blood 2014;124:188-195

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 ≥ 38^{0}C	Yes	Any	Any	Any
	SBP < 90	No	Responds to IV fluids or low-dose vasopressor	Needs high-dose or multiple vasopressors	Life- threatening
	Needing oxygen for O_2 sat >90%	No	FiO2 <40%	FiO2 ≥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 CTCAE, version 4 for grading of organ toxicity.

Adapted from Lee et al, Blood 2014;124:188-195

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**	• 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 filgrastim if neutropenic • IV fluids as needed • Symptomatic management of constitutional symptoms and organ toxicities
Grade 2	**Hypotension**	• 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	• 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	• Manage organ toxicity as per standard guidelines • Use tocilizumab +/- corticosteroids as in hypotension • Manage fever and constitutional symptoms as in Grade 1 CRS

Step 3 – Manage CRS and organ toxicity

CRS Grade	Symptom or Sign	Management
Grade 3	**Hypotension**	• 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	• 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	• 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**	• Manage as in Grade 3 CRS
	Hypoxia	• Mechanical ventilation
	Grade 4 organ toxicity excluding transaminitis	• 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

Step 2 – Determine the 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	Obtundation 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	
Institution specific grading?				

Step 3 – Manage neurotoxicity

Grade	Management
Grade 1	• Vigilant supportive care; Aspiration precautions • Daily simplified neurologic examination • 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 • Consider Tocilizumab 8 mg/kg IV if associated with Grade 2 or greater CRS
Grade 2	• Manage as per Grade 1 • Consider ICU transfer if associated with Grade 2 or greater CRS • Tocilizumab 8 mg/kg IV if associated with Grade 2 or greater CRS
Grade 3	• 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, • 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	• 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 • High grade (3, 4, & 5) papilledema, CSF op ≥ 20 mm Hg, or cerebral edema