2023 Oncology Fellows Program:
New Horizons in Quality Cancer Care™

Team-Based Management of Immunotherapy-Related Toxicities

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ICI GI toxicity

GI Toxicity Case

- 60 y/o female with metastatic kidney cancer, received ipilimumab and nivolumab for 4 doses
- Developed significant diarrhea (CTCAE grade 2; 5 times/day, watery stool) week after C4, with no other symptoms

Polling Question #1

Given the presentation of your patient, what is the best initial step in management?

1. Start empiric antibiotics for suspected infectious colitis
2. Order stool infectious and inflammatory work-up
3. Schedule patient for endoscopy as soon as possible
4. Start steroids for suspected immune-related GI toxicity
5. Prescribe antimotility agents and follow-up in one week

Laboratory work-up

Test	Purpose	Value
GI Multiplex	Rule out infection	Negative
C. difficile DNA	Rule out infection	Negative
Fecal Lactoferrin	Marker of intestinal inflammation	Abnormal
Fecal Calprotectin	Marker of intestinal inflammation	Elevated (560, Normal <50)

Disease Course #1

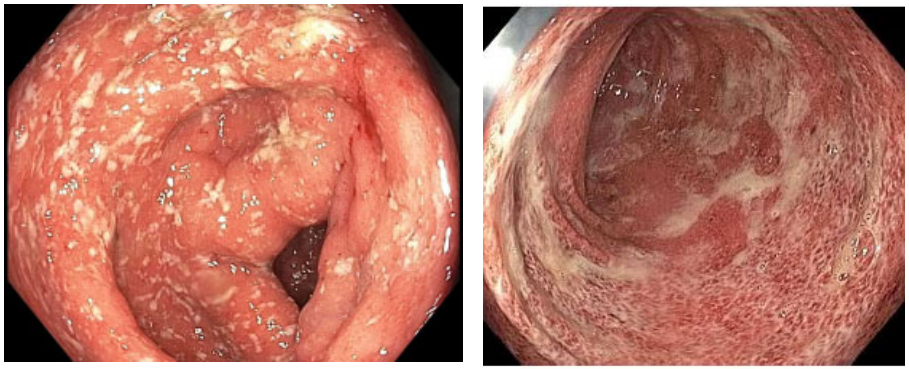
- While completing the work up, patient tried anti-motility medications.
- However, symptoms rapidly progressed within 1 week.
- Now bloody diarrhea 10 times/day with mucus, abdominal pain.

Polling Question #2

What is the appropriate next step of managing this patient?

1. Hospital admission, endoscopic evaluation, and start intravenous steroid
2. Oral steroid with close outpatient follow up as patient is clinically stable
3. Oral hydration, PPI, check CBC, transfuse as needed
4. Urgent outpatient GI consult in one week

Endoscopic Evaluation



Erythema, congestion, friability, ulceration.

Path: acute colitis with negative CMV.

Polling Question #3

Which of the following endoscopic features is most concerning for more severe disease?

1. Ulceration
2. Edema
3. Exudate
4. Erythema
5. None are prognostic

Disease Course #2

- Patient was admitted.
- Symptoms persisted after 2 days of iv steroid (1mg/kg).
- Then 1 dose of infliximab 5mg/kg was added.
- 2nd dose of infliximab 10mg/kg was given 2 weeks later as well as continuous iv steroid without improvement.
- Patient remained hospitalized.

Polling Question #4

Which of the following is the most appropriate next step?

1. Continue infliximab 3rd dose in 2 weeks in addition to iv steroid
2. Switch to vedolizumab
3. Continue high dose steroid alone with close observation
4. Repeat colitis work up to rule out infections (including repeat colonoscopy)

Laboratory Work-Up

Test	Value
GI Multiplex	Negative
C. difficile DNA	Negative
Calprotectin	Elevated (2350)
CMV in colon biopsy	Positive

Discussion Question #5

Which of the following is most appropriate for this patient?

A. Start antiviral for CMV infection, and ID consult

B. Hold all the colitis treatments including steroid, infliximab

C. Start antiviral and continue steroid/infliximab concurrently

D. Options A and B

Disease Course #3

- Symptom of diarrhea 5-7 times/day with bleeding persisted despite 7 days of IV ganciclovir.
- She reported even worsening diarrhea symptoms with this treatment and refused further doses.
- She was treated with vedolizumab, the alternative treatment for colitis (α4β-7 integrin blocker used to treat inflammatory bowel disease).
- Then she developed severe infectious sinusitis and diffuse arthralgia, likely related to vedolizumab.

Discussion Question #6

Which of the following is the most appropriate next step?

A. Complete 2-week course of CMV treatment

B. Continue 2nd dose of vedolizumab treatment 2 weeks later after controlling sinus and joint symptoms

C. Change treatment to ustekinumab (IL12/23 inhibitor used to treat Crohn's and Ulcerative colitis)

D. Offer fecal microbiota transplant (FMT)

Disease Course #4

- Patient refused more doses of ganciclovir and vedolizumab with some symptom improvement after first vedolizumab dose.
- Flexible sigmoidoscopy was negative for CMV, but confirmed persistent colitis.
- Started ustekinumab as outpatient with more symptom response, and achieved remission after 2nd dose 2 months later, then developed sinus congestion/sinus infection right after 2nd dose. Steroid was stopped after first dose of ustekinumab.
- Ustekinumab was discontinued, with colitis symptom in remission for 3 months with no immunosuppressant.
- Then patient had recurrent grade 3 diarrhea (>10 loose BM/day) and grade 2 colitis (bleeding and mucus in the stool) despite off ICI for total 5 months.

Disease Course #5

- While colitis flare up, kidney cancer progression was also identified on surveillance imaging.
- Given the previous excellent response to immune checkpoint therapy, the patient is very eager to restart treatment.

Discussion Question #7

Which of the following is the most appropriate for this patient?

A. Re-challenge vedolizumab and restart nivolumab alone

B. Re-challenge ustekinumab and restart nivolumab alone

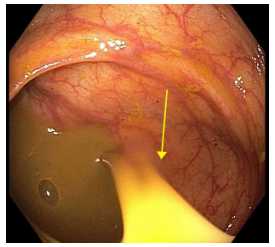
C. Try FMT and restart nivolumab alone

D. Any of the above and restart both nivolumab and ipilimumab

E. Offer alternate anticancer therapy given the inability to safely re-challenge immune checkpoint therapy.

Disease Course #7

- Patient received fecal transplant treatment via colonoscopy.
- Colitis symptoms resolved one week post-transplant.
- Nivolumab was subsequently restarted 2 weeks after FMT and continued for 12 months, with no recurrence of colitis or other irAE.
- Both clinical and endoscopic remission of colitis was achieved in the disease course on the routine follow up assessment, and kidney cancer remained controlled.



Case Summary

- 60 yo F with kidney cancer received ipilimumab and nivolumab, developed moderate colitis which rapidly progressed to severe colitis with ulceration identified during endoscopy.
- Colitis course was refractory to infliximab/steroid, complicated with CMV infection, and the patient was intolerant to vedolizumab/ustekinumab despite mild clinical improvement.
- Cancer progression was identified after interruption of ipi/nivo, prompting the need for treatment re-challenge despite persistent colitis.
- Fecal transplant achieved sustained colitis remission and enabled successful resumption on nivolumab with a favorable cancer outcome.

Review Points

- Stool lactoferrin and calprotectin can be useful to screen and monitor colitis status for colitis severity.
- Endoscopy with biopsy can provide more accurate severity assessment for colitis than CTCAE grade on symptoms alone.
- High risk endoscopic features (ulcers, and extensive colitis beyond left colon) are associated with more refractory colitis disease course.
- Early introduction of steroid-sparing immunosuppressant agents (e.g. infliximab, vedolizumab) may hasten resolution of colitis.
- Endoscopic remission (with resolution of visible inflammation) is associated with lower colitis recurrence, should be considered as treatment target.
- Fecal transplant can be an effective treatment for refractory colitis by altering the microbiome.

3M toxicity

Clinical Case

- 53 year-old man with metastatic nasopharyngeal carcinoma received neoadjuvant pembrolizumab followed by surgical resection of 2 isolated metastasis 3 weeks later.
- On post-op day 2 he reported new binocular horizontal diplopia. On neurologic exam he was noted to have R eye ptosis and limited bilateral abduction and R eye adduction. No other weakness noted on exam. No respiratory or other symptoms.
- Neurology was consulted. MRI brain and MRA head and neck were performed to rule out vascular etiology and returned normal. Myasthenia gravis labs (AChR abs) are sent.

Disease Course #1

- The next day, the patient reported stable eye symptoms but new heaviness in his bilateral shoulders and neck. He has difficulty holding his head up when using the toilet. Some shortness of breath. He feels better sitting in chair as compared to bed.

Polling Question

What is the appropriate next step of managing this patient?

1. Check NIF/VC, start pyridostigmine for suspected myasthenia gravis, schedule urgent outpatient EMG/NCS
2. Obtain MRI brain with thin cuts of brainstem
3. Perform lumbar puncture to evaluate for leptomeningeal metastasis
4. Check CPK, trop, and EKG

Disease Course #2

- The team orders a bedside NIF/VC and a CPK. NIF/VC is normal.
- Overnight, the patient develops bradycardia. ECG shows NSR with complete heart block, ST elevation, wide complex rhythm. Trop sent and returns along with the CPK
- CPK: 5100 Troponin I: 32.2 ng/mL

Disease Course #3

- Transferred to cardiac ICU. Undergoes left heart catheterization 70% coronary obstruction found stented, but continued to have VT/complete heart block, requires temporary external pacing.
- Undergoes right heart catheterization with endomyocardial biopsy. Pathology: predominant histiocytic myocarditis with focal lymphocytes.

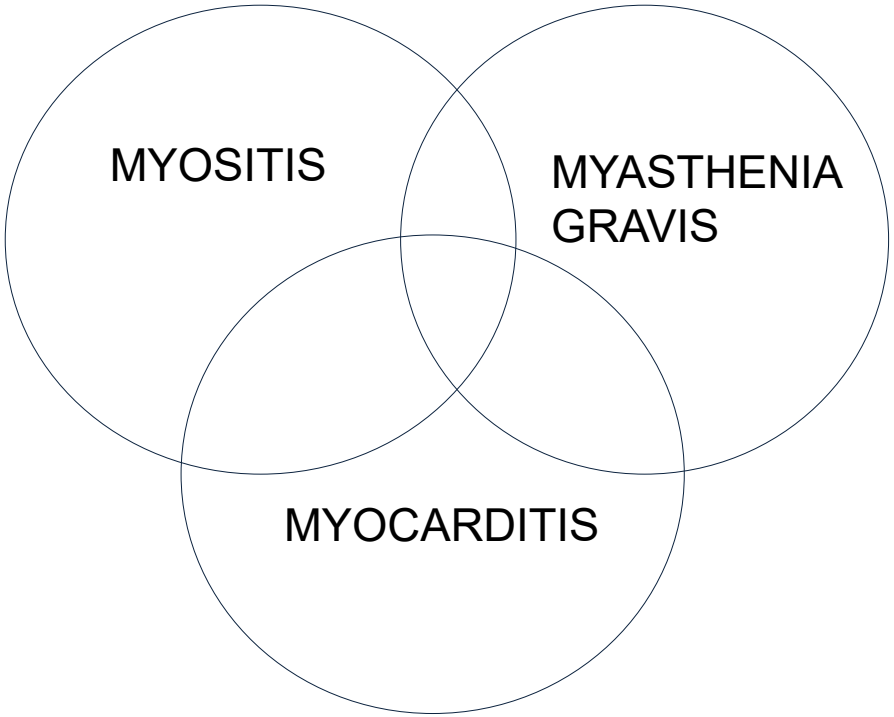
ICI-Myocarditis

- Biopsy: T cell and macrophage infiltration in striated muscle (may be risky). May also assess with cardiac MRI
- ECG abnormalities
- Arrythmia
- Ejection fraction may be preserved. TTE not as helpful as ECG/trop

- Who and when:
- Early and unpredictable
- 30-50% case fatality
- Combination ICI is main risk factor: 2% with dual ICI, 1% with mono

Moslehi et al. Lancet 2018

3M Toxicity



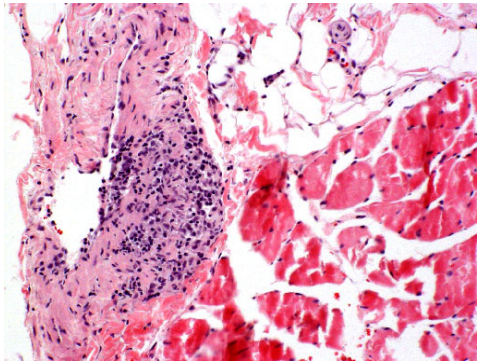
When you encounter or suspect one diagnosis, send workup for all 3

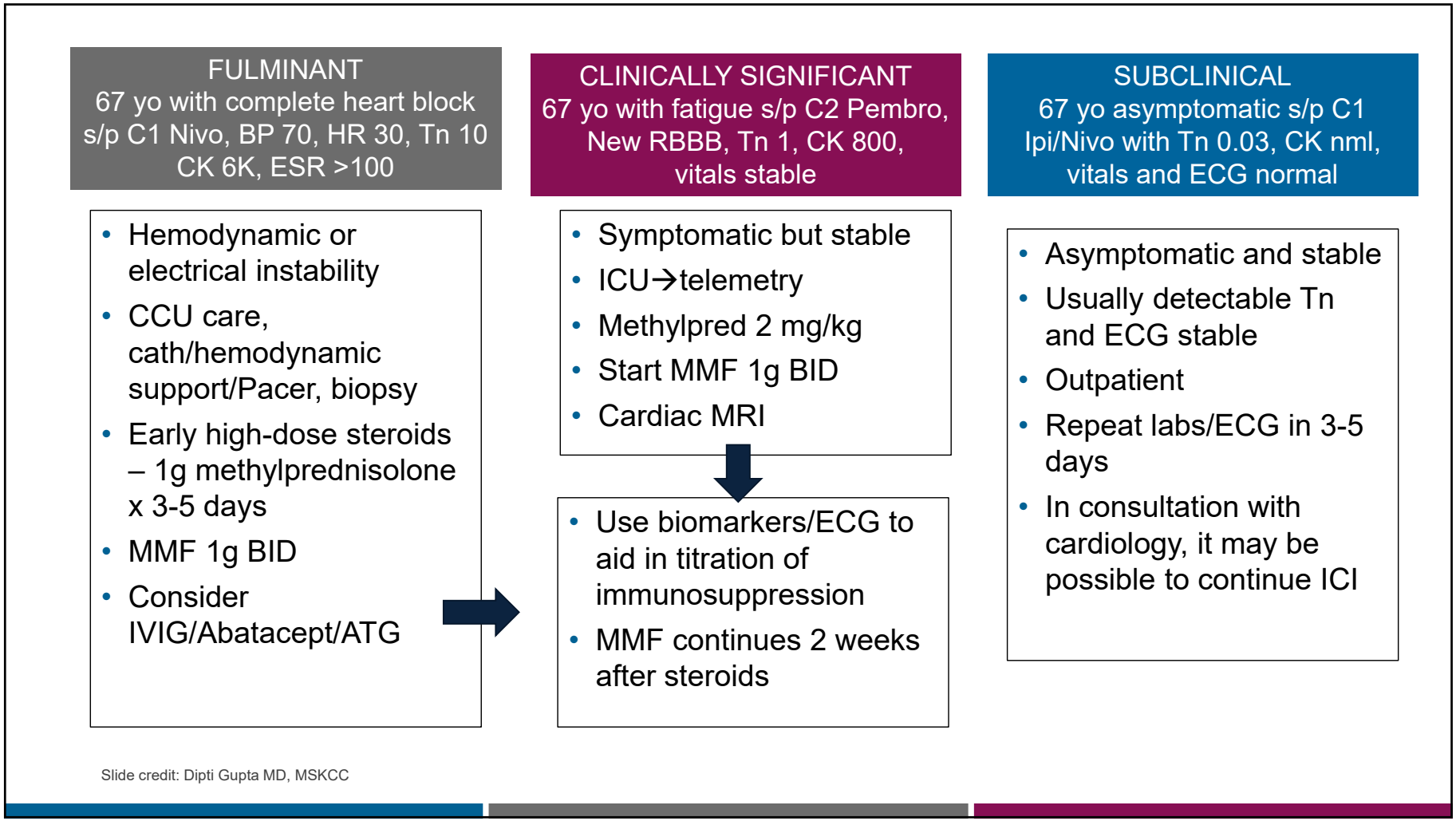
“3M”: Myositis/Myocarditis/Myasthenia Gravis

- He is started on pulse-dose (1 gram) IV methylprednisolone and is placed on mycophenolate.
- He responds and, after 3 days of pulse-dose steroids, is switched to oral prednisone (1mg/kg/day) which is slowly tapered over 8 weeks using biomarkers/ECG to aid in titration.
- His symptoms gradually improve. CPK and trop normalize. EKG changes resolve. Myasthenia gravis panel returns negative.

“3M” irAE

- Usually in the first 2 months after ICI initiation
- Ocular and bulbar symptoms are frequent, even in isolation
- Weakness in limbs (proximal) and neck muscles “dropped head”
- CPK, aldolase, AST, ALT levels often, but not always, elevated
- May see mild decrement on rep stim. It is usually absent.
- Anti-AChR antibodies seen in up to a quarter of patients
- Myositis-specific antibodies usually absent. May see anti-striated muscle antibodies
- Histology muscle biopsy shows focal clusters of necrotizing myopathy and endomysia immune infiltrates (mostly macrophages and T cells
- Fatality mostly due to concomitant myositis or respiratory involvement



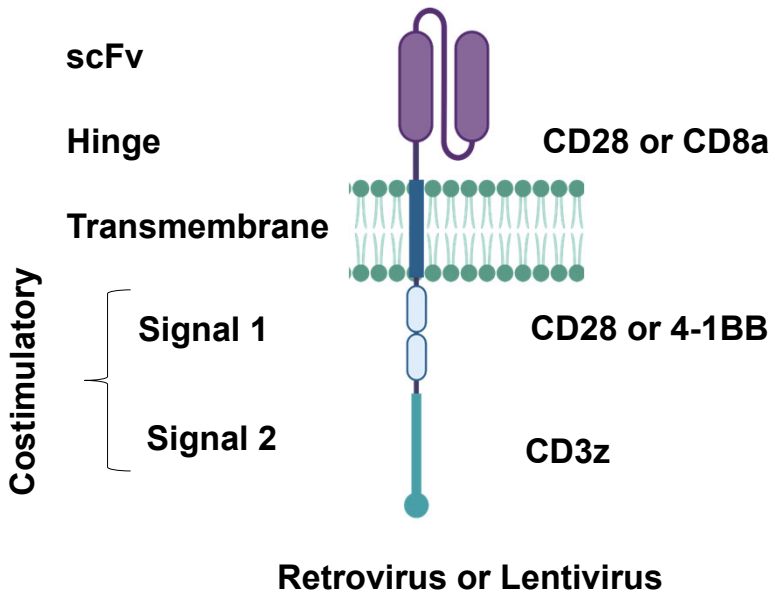


Review Points

- Timing of 3M is typically early ~ 8 weeks
- Risk factor is combination therapy, but may occur with monotherapy
- Symptoms may be variable and there may be rapid progression
- Myocarditis: Heart block, VT and sudden death feared.
- Myositis/MG: respiratory insufficiency feared
- When you encounter or suspect one diagnosis, send workup for all 3
- Symptoms of one of the triad may emerge during steroid taper/recovery from an initial toxicity (MG emerging after treatment for myocarditis)

CAR T-Cell Toxicities

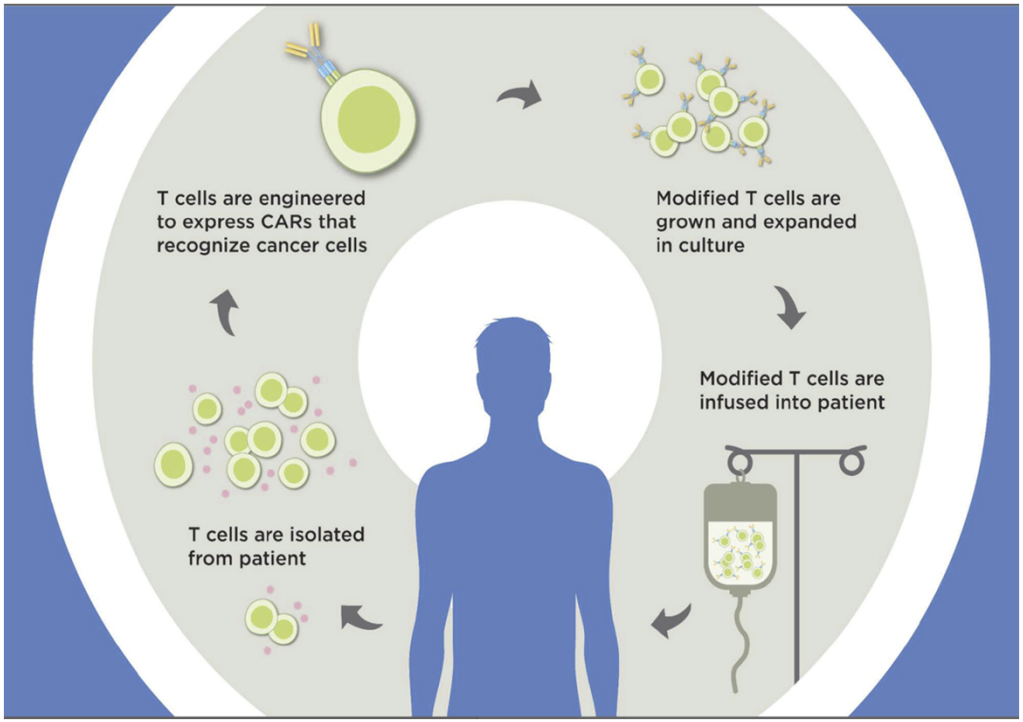
General Structure of a Chimeric Antigen Receptor (CAR)

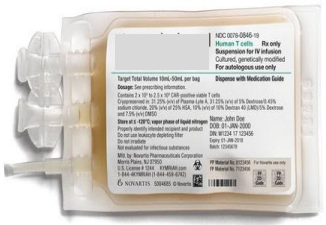


Domains:

- **ScFv**: Recognizes a specific tumor antigen
- **Hinge and Transmebrane**: Connects the scFv to the rest of the CAR
- **Intracellular**: Contains two domains that provide costimulatory signals to activate the CAR T cell after it recognizes a tumor antigen through the scFv
- The CAR construct is packaged in a retrovirus or lentivirus and then transduced to the T cell

Chimeric Antigen Receptor (CAR) T Cell Therapy





mskcc.org

There are 6 FDA approved CAR T cell products in the US

	Indication	Product
CD19 CAR	ALL: Pediatric and young adults (up to age 25)	Tisagenlecleucel (tisa-cel)
CD19 CAR	R/R large B cell lymphoma (LBCL, tFL, MZL, +/- PMBCL)	Tisa-cel Axicabtagene ciloleucel (axi-cel) Lisocabtagene maraleucel (liso-cel)
CD19 CAR	R/R follicular lymphoma	Axi-cel Tisa-cel
CD19 CAR	R/R Mantle cell lymphoma	Brexucabtagene autoleucel (brexu-cel)
CD19 CAR	ALL; Adults with R/R B-ALL	Brexu-cel
BCMA CAR	R/R Multiple myeloma	Idecabtagene vicleucel (ide-cel)
BCMA CAR	R/R Multiple myeloma	Ciltacabtagene autoleucel (cilta-cel)

Potent therapy, but associated with unique toxicities

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

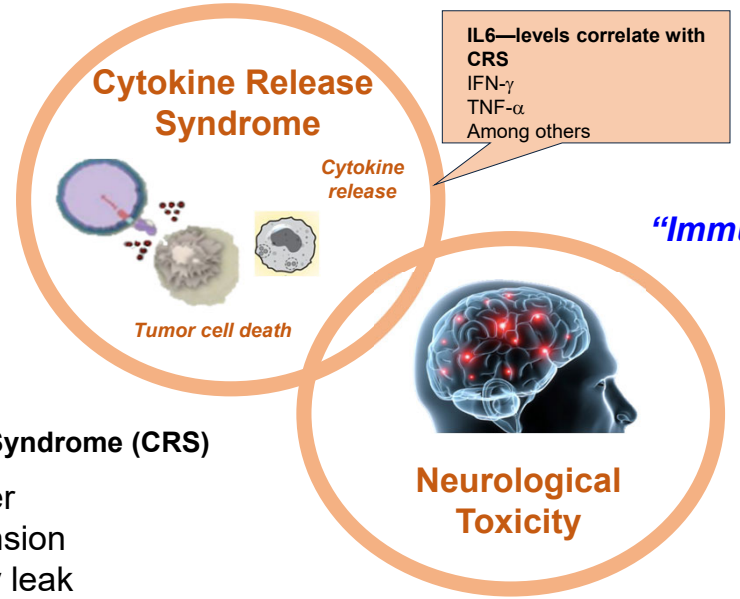
See full prescribing information for complete boxed warning.

Toxicity rates with commercially approved products*

CRS all grades	**42% - 95%**
G ≥3 CRS	**1% - 23%**
Neurotoxicity all grades	**12% – 63%**
G ≥3 Neurotoxicity	**3% - 31%**

- Patients may require ICU management
- Fatalities have occurred
- **Risk Evaluation and Mitigation Strategy (REMS)** mandated for CRS and Neurotoxicity
  - Dedicated prescribers who are trained in the toxicities
  - Ensure that hospitals and clinics have immediate access to tocilizumab

**Locke et al. The Lancet Onc, 2019; Jacobson et al. The Lancet 2021; Locke et al. NEJM 2022; Abramson et al. The Lancet 2020; Kamdar et al. The Lancet 2020; Wang et al. NEJM 2020; Shah et al. The Lancet; Maude et al. NEJM 2018; Schuster et al. NEJM 2019; Fowler et al. Nat Med 2022; Munshi et al. NEJM 2021; Berdeja et al. Lancet 2021*



Cytokine Release Syndrome (CRS)

Fever
Hypotension
Capillary leak
Respiratory insufficiency
Hyperferritinemia/MAS
Coagulopathy/DIC
Multi-organ failure

Symptoms rapidly resolve with IL-6R blockade

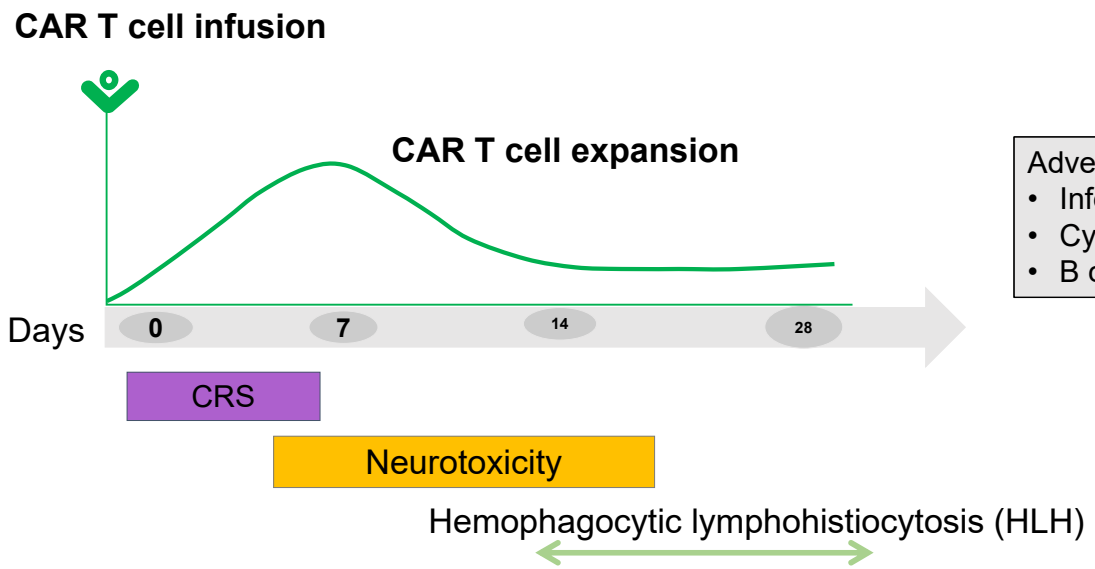
Neurotoxicity

"Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)*"

Global encephalopathy
Word Finding Difficulty/Aphasia
Tremor
Somnolence
Seizure, seizure-like activity
Agitation/Hallucinations
Motor weakness
(Rapid Onset Cerebral Edema)

Symptoms do not resolve with IL-6R blockade

CAR T Toxicities Timeline



Adverse Events > Day 30
- Infections
- Cytopenias
- B cell aplasia

Clinical Case Severe CAR T Toxicity

- 57 y/o male with relapsed refractory large B cell lymphoma received Cy/Flu preconditioning followed by axicabtagene ciloleucel (axi-cel)

- On day 2 post infusion, he developed high fever 39.5°C and tachycardia to 120s. He received an IV fluid bolus for hypotension and developed an increased O2 requirement (4L/min NC). Mental status and neurologic exam were normal. Meets criteria for Grade 2 CRS.

Clinical Case Severe CAR T Toxicity

- Cultures sent and empiric antibiotics are started. Cardiac telemetry is started. Tocilizumab is administered for Grade 2 CRS and his fever, tachycardia, and hypoxia resolves within hours.
- On day 5 post-infusion he develops new perseverative/stuttering speech, inattention, and somnolence. There are no signs or symptoms of CRS and C-reactive protein is normal.
- Word finding difficulty progresses over the course of 8 hours to his being awake, but globally aphasic.
- Neurology is consulted and a non-contrast CT brain and electroencephalogram (EEG) are performed and are negative. Prophylactic Levetiracetam, which was started at infusion, is continued. He is transferred to the ICU.

Polling Question

What is the most appropriate next step in pharmacologic management of this patient?

1. Start intravenous corticosteroids
2. Administer repeat dose of tocilizumab
3. Administer tocilizumab plus intravenous corticosteroids
4. Increase levetiracetam dose

Clinical Case Severe CAR T Toxicity

- He is started on dexamethasone 10 mg IV every 6 hours
- His mental status continues to decline over the 8 hours. In addition to global aphasia, he now has depressed level of consciousness arousable only to persistent tactile stimulus.

Discussion Question

Which of the following is most appropriate for this patient?

A. Continue dexamethasone 10 mg IV every 6 hours for grade 3 ICANS

B. Continue dexamethasone 10 mg IV every 6 hours for grade 4 ICANS

C. Switch to methylprednisolone 1G IV q 24h for grade 3 ICANS

D. Switch methylprednisolone 1G IV q 24h for grade 4 ICANS

Clinical Case Severe CAR T Toxicity

- He is switched to methylprednisolone 1G IV every 24 hours for Grade 4 ICANS. A lumbar puncture is performed. The opening pressure is normal. CSF shows slightly elevated cell count, markedly elevated protein level, and negative infectious panel
- After 2 days/doses of pulse-dose methylprednisolone his level of consciousness and aphasia improves.
- Steroids are tapered rapidly over the next 4 days as his mental status continues to improve.
- By day 16 he has returned to baseline mental status.

Grading and Management of CRS

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
ASTCT CRS Consensus Grading, adapted from Lee et al. BBMT 2019	Temperature ≥ 38°C No hypotension No hypoxia	Temperature ≥ 38°C with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula (≤ 6L/min)	Temperature ≥ 38°C with hypotension requiring vasopressors +/- vasopressin and/or hypoxia requiring high -flow nasal cannula (>6L/min), facemask, nonrebreather mask, or Venturi mask	Temperature ≥ 38°C with hypotension requiring vasopressors excluding vasopressin and/or hypoxia requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)
CRS Management Guidelines NCCN	• Supportive care • Rule out infection • Consider tocilizumab if fever is refractory to above measures for > 3 days or in high-risk patients/products	• Supportive care per G1 • Initiate cardiac telemetry IV fluid for hypotension • Tocilizumab up to 3 doses per day • Consider initiating dexamethasone 10 mg q 12-24 h if no response to 1-2 doses of tocilizumab	• As per G2 • Assess cardiac function using ECG, ICU transfer, vasopressors as needed • Dexamethasone 10 mg q 6 -12h depending on the product	• Per G3 • ICU transfer • Methylprednisolone 1-2g/day • If no response consider alternate immunosuppressant (anakinra, cyclophosphamide, ATG, and others)

Grading of ICANS: ASTCT Consensus Encephalopathy Assessment Tool

Immune-Effector Cell-Associated Encephalopathy (ICE) Tool
• **Orientation:** Orientation to year, month, city, hospital: 4 points • **Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points • **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 ten: 1 point Score 10: No impairment 7-9: grade 1 3-6: grade 2 0-2: grade 3 0 due to patient unarousable and unable to perform ICE: grade 4

Cornell Assessment of Pediatric Delirium (CAPD) used for children under age 12

Lee, Santomasso et al. Biol Blood Marrow Transplant, Dec 2018

Grading of ICANS - 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 et al. Biol Blood Marrow Transplant, Dec 2018

Assessment of ICANS

- Baseline exam including ICE
- Neurologic assessment at least twice a day to include cognitive assessment (ICE) and motor weakness
- Neurology consult at first sign of neurotoxicity
- MRI of the brain, or CT if MRI not feasible for ≥ grade 2 neurotoxicity
- EEG for ≥ grade 2 neurotoxicity to evaluate for seizure activity
- Use caution when prescribing medications that can cause CNS depression (aside from those needed for seizure prophylaxis/treatment)

Management of ICANS

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Treatment by Grade	No Concurrent CRS[X]
Grade 1[V]	• Supportive care
Grade 2	• Supportive care • 1 dose of IV dexamethasone 10 mg and reassess. Can repeat every 6–12 hours, if no improvement.
Grade 3[W]	• ICU care is recommended • IV dexamethasone 10 mg every 6 hours or IV methylprednisolone, 1 mg/kg every 12 hours[K,Y] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.
Grade 4[W]	• ICU care, consider mechanical ventilation for airway protection. • High-dose steroids[K,Z] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

- For liso-cel or ida-cel, if ICANS develops less than 72h post infusion, consider dex 10 mg IV every 12-24 h x 2 doses
- For axi-cel or brexu-cel methylprednisolone 1G daily for 3-5 d may be preferable management for G3
- For axi-cel, cilta-cel, or ide-cel consider dex 10 mg IV starting at grade 1*

*Axicabtagene ciloleucel prescribing information, ciltacabtagene autoleucel prescribing information, idecabtegene vicleucel prescribing information

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Review Points

- Cytokine release syndrome and neurotoxicity, known as ICANS, are the 2 most common toxicities occurring in patients receiving CAR T cell therapy
- CRS and ICANS are graded using the ASTCT consensus grading
- The mainstay of CRS management is the IL6R blocker tocilizumab, which is FDA approved for this indication. Corticosteroids may be used in addition to tocilizumab for severe cases.
- Tocilizumab has no role in the management of isolated ICANS
- ICANS is managed with supportive care and corticosteroids
- Anakinra (IL1 RA) and other medications may be considered for CRS and ICANS that is refractory to steroids

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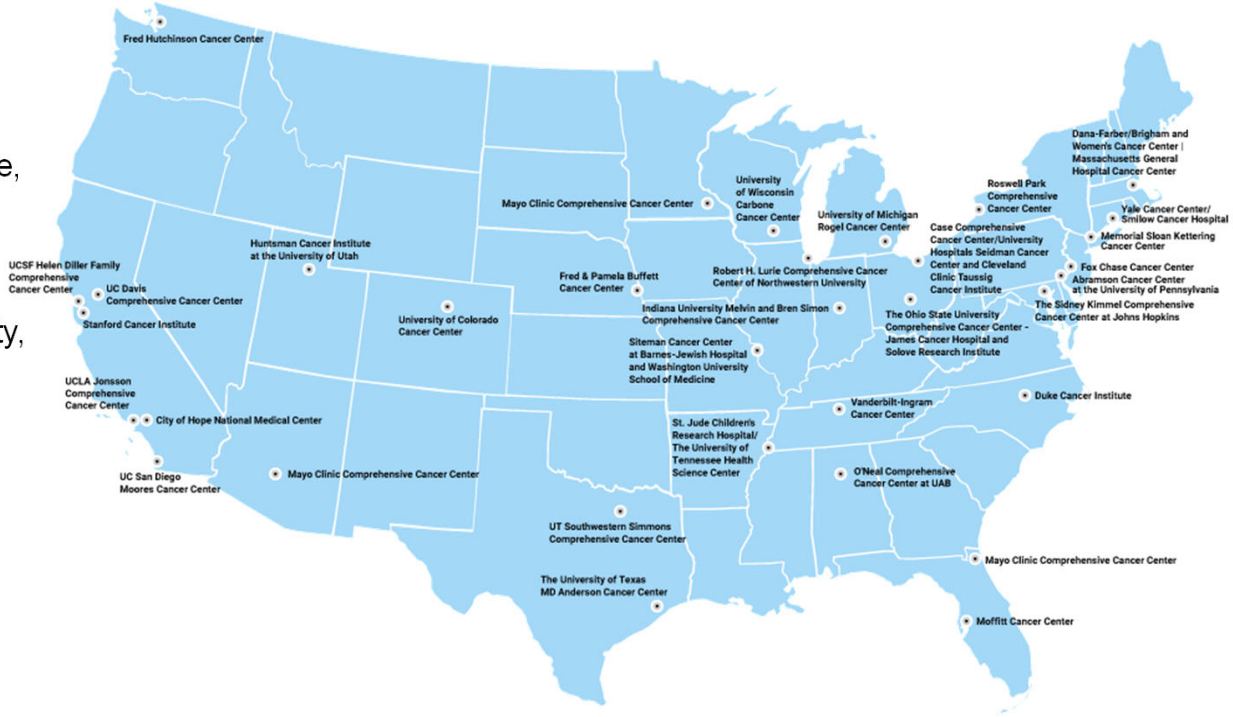
  To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



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