Overview of CAR-T and Checkpoint Inhibitor Therapy

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Disclosures

- No relevant financial relationship(s) exist
- Some off label use and/or investigational use of toxicity therapy will be mentioned. When this occurs it will be clearly identified as such.

Objectives

- Describe the cellular engineering and mechanism of action of CAR-T cells
- Describe chemotherapy conditioning and patient selection for CAR-T therapy
- Explain manifestations and management of adverse effects of CAR-T therapy including cytokine release syndrome and neurologic toxicity
- Describe what checkpoint inhibitors are used for and their mechanism of action
- Explain manifestations and management of immune mediated effects of checkpoint inhibitors including thyroid dysfunction, colitis, and other toxicity

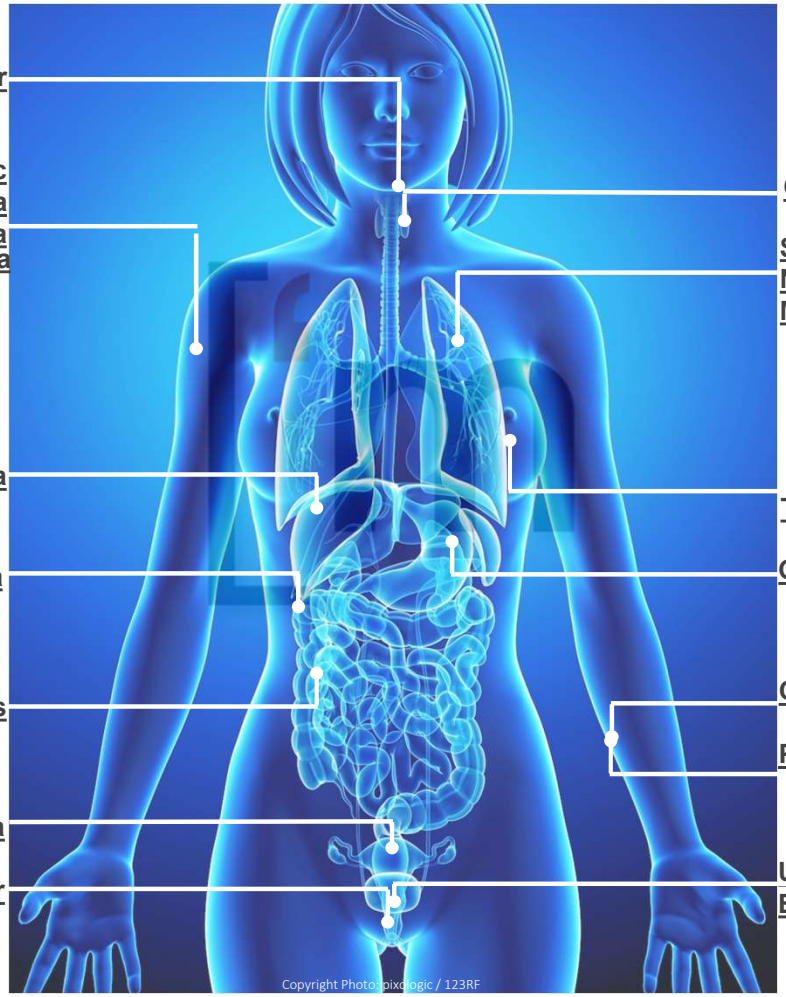
Checkpoint Inhibitors

- **PD-1 inhibitors:**
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

- **PD-L1 inhibitors:**
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

- **CTLA-4 inhinbitor:**
- Ipilimumab (Yervoy)

U.S. FDA Approved Immune-Checkpoint Inhibitors



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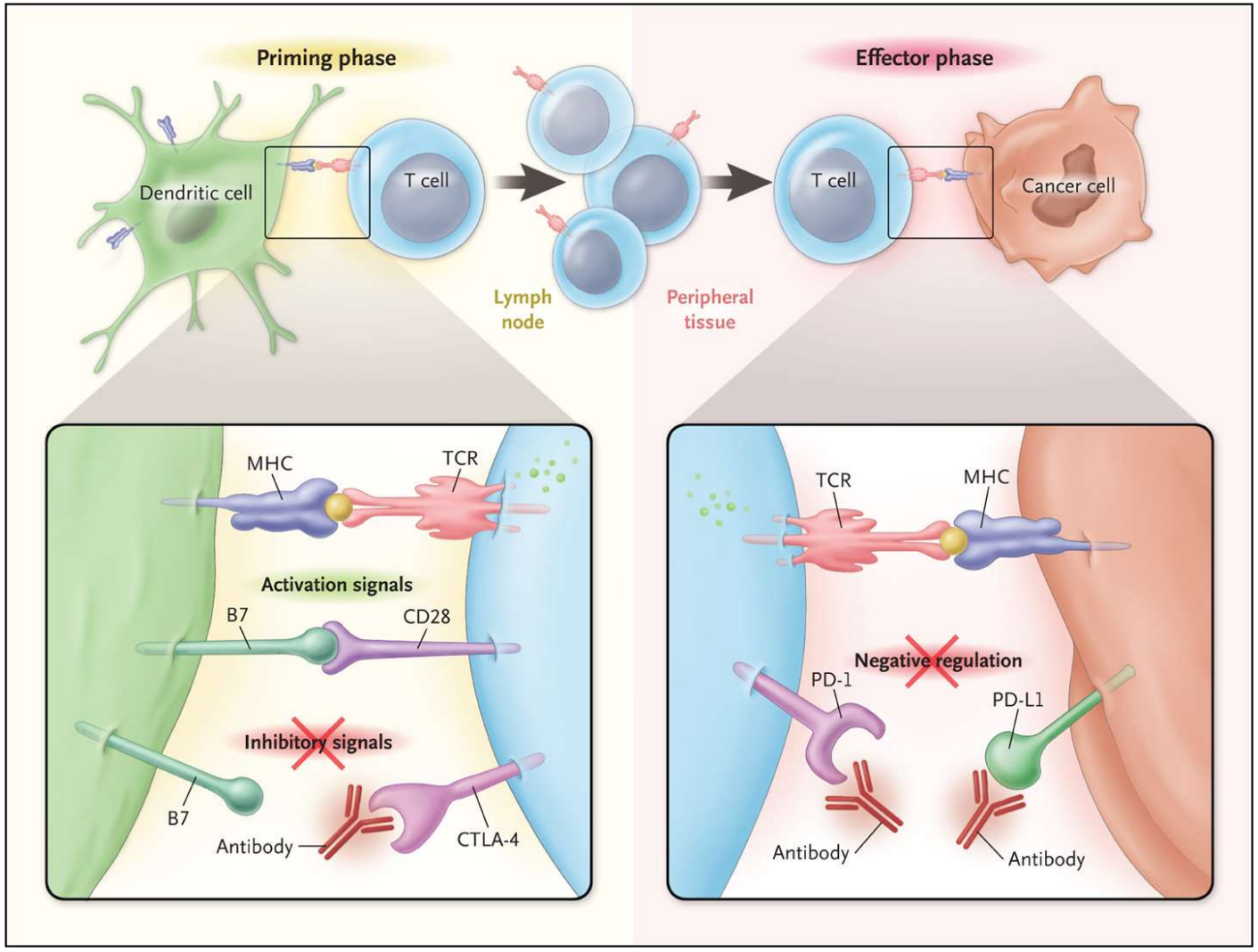
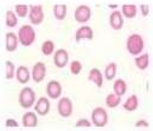
Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy

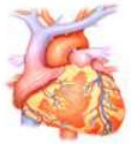


Ribas A. N Engl J Med 2012;366:2517-2519.

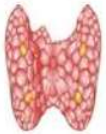
Toxicities Associated with Checkpoint Inhibitors



BLOOD
Haemolytic anaemia
Thrombocytopaenia
Neutropenia
Haemophilia



CARDIOVASCULAR
Myocarditis
Pericarditis
Vasculitis

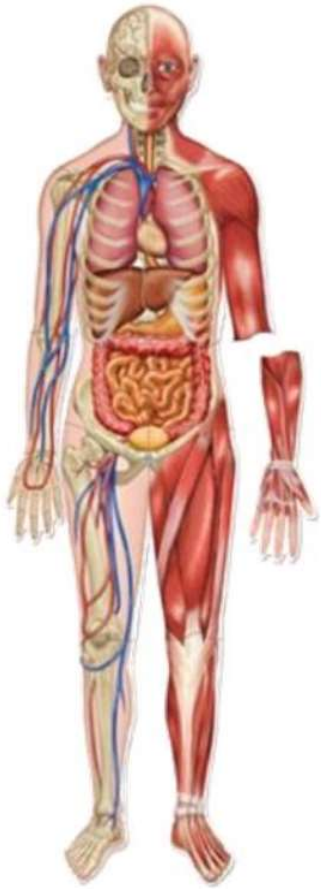


ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Hypoadrenalism
Type 1 diabetes

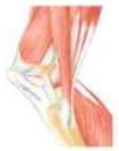
EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

GASTROINTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

LIVER
Hepatitis



MUSCULOSKELETAL
Dermatomyositis
Arthritis

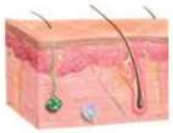


NEUROLOGICAL
Neuropathy
Guillain Barre
Meningitis
Encephalitis
Myasthenia

RENAL
Nephritis

RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like
granulomatosis

SKIN
Rash
Pruritis
Psoriasis
Vitiligo
DRESS
Stevens Johnson



https://cancerforum.org.au/forum/2018/april/cancer-immunotherapy-at-a-new-immune-frontier/

- How common are IrAE?
- Which IrAE are the most common?
- When do you typically see IrAE?

Endocrine Related Adverse Events

- The thyroid, adrenal, and pituitary glands are the organs primarily impacted
- TSH/T4 monitoring
- More common w/ ipilimumab

Hypophysitis

Chang, Checkpoint inhibitor Associated Hypophysitis. JGIM 2018 Jun 10;36

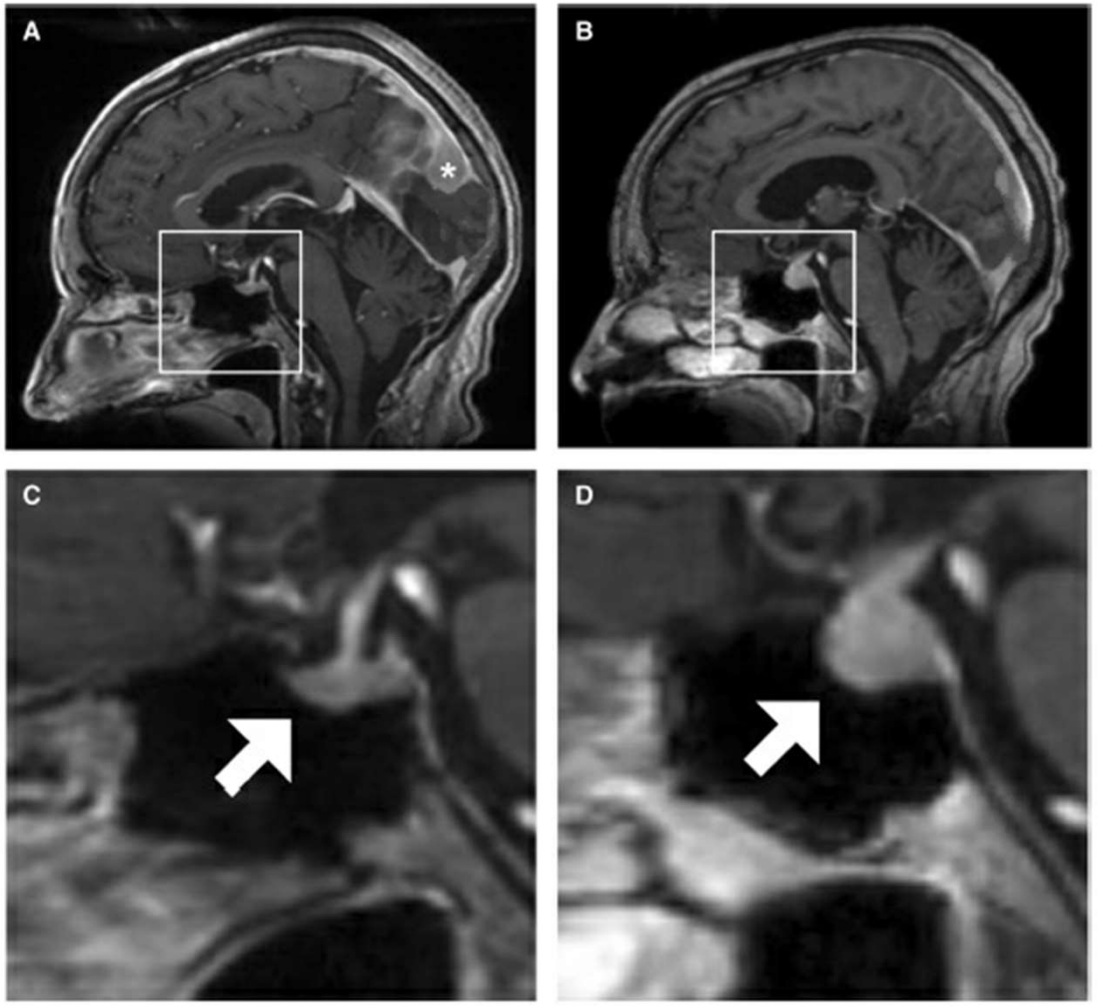


Figure 2 Sagittal views of the patient's brain on MRI. A Before ipilimumab and nivolumab initiation. The patient had a preexisting parafalcine meningioma (*asterisk*). B Five months after ipilimumab and nivolumab initiation. C Inset of panel A, with a normal-sized pituitary gland (*arrow*) and pituitary stalk. D Inset of panel B, with diffuse enlargement of the pituitary gland (*arrow*) and thickening of the pituitary stalk.

Neurologic toxicities

- Polyneuropathy
- Guillen barre syndrome
- Myasthenia Gravis
- Myositis
- Encephalitis
- Meningitis
- Transverse Myelitis

Toxicities - Management

- Evaluation and Management
  - Site specific
  - Steroids initial Tx for most toxicities
  - If unresponsive, Tx may include
    - MMF
    - Azathioprine
    - Cyclosporine
    - Infliximib
    - IVIG/Plasmapheresis

Case study 1

- 72 y/o M w/ 2B cutaneous melanoma w/ resection. 10 mo later 2 new lesions on back wide resection and axillary LN. No braf mutation so started on nivolumab
- 6 cycles nivolumab POD w/ new LN involvement in the mediastinum.
- Now ipilimumab started, just after 4th dose admitted w/ fever to 101 F and failure to thrive

- (grade 4 elevation of aspartate transaminase (AST): 783 IU/L, grade 4 elevation of alanine transaminase (ALT): 1029 IU/L, grade 2 elevation of gamma-glutamyl transferase (GGT): 147 IU/L, grade 2 elevation of bilirubin: 1.9 mg/dL)
- Viral causes of hepatitis (eg, hepatitis A, B, C and E viruses, cytomegalovirus, Epstein-Barr and herpes simplex viruses as well as HIV) were excluded and serological assessment for autoimmune hepatic disease, including antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), antismooth muscle antibodies (SMA), antiliver-kidney microsomal antibodies (LKM) and antisoluble liver antigen (SLA), was negative.

- adrenocorticotropic hormone=5 pg/mL (10–65 pg/mL),
- cortisol=209.72 mmol/L (173.6–505 mmol/L),
- prolactin=8.69 ng/mL (7–23 ng/mL),
- follicle stimulation hormone=2.39 mIU/mL (3.5–9.2 mIU/mL),
- luteinizing hormone=3 mIU/mL (1.9–9.2 mIU/mL),
- testosterone=0.64 ng/mL (1.93–7.40 ng/mL) and

Treatment of patient

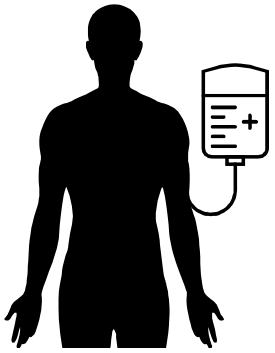
- 1mg/kg of methylprednisolone started given liver, 4 days later it worsened and inc to 2mg/kg
- 3 days later not improving MMF, added tacrolimus.
- Could consider infliximab as well
- 60+ d hospital course prednisone .75mg/kg d/c

Chimeric Antigen Receptor (CAR) T cell

CAR T-Cell Therapy: Underlying Principles

Leukapheresis

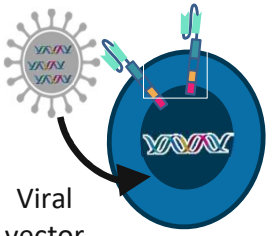
Collect patient's white blood cells

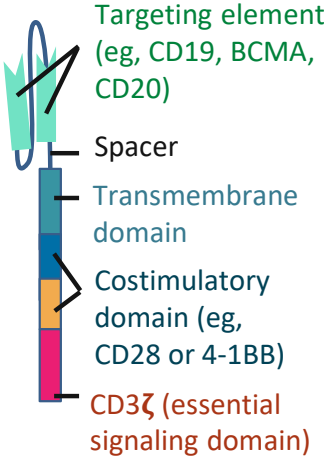


Manufacturing

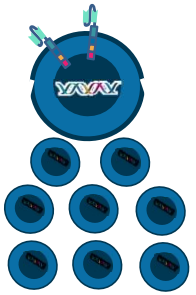
Isolate and activate T-cells

Engineer T-cells with CAR gene





Expand CAR T-cells

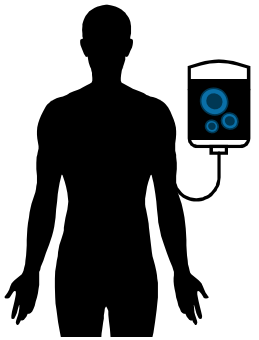


Median manufacturing time: 17-28 days

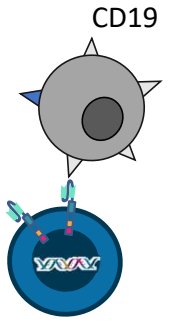
Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Infusion

Infuse same patient with CAR T-cells



Activity



Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

FDA-Approved CAR T-Cell Therapies

Therapy	Target	Indications
Tisagenlecleucel	CD19	▪ **Patients aged up to 25 yrs with B-cell precursor ALL that is refractory or in second or later relapse** ▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy**, including DLBCL NOS, DLBCL arising from follicular lymphoma, high-grade B-cell lymphoma
Axicabtagene ciloleucel	CD19	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy,** including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma
Brexucabtagene autoleucel	CD19	▪ **Adults with R/R MCL**
Lisocabtagene Maraleucel	CD19	▪ **Adults with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy,** including DLBCL NOS, DLBCL arising from follicular lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI. 3. Brexucabtagene autoleucel PI.

Slide credit: clinicaloptions.com

Acute CAR-T Toxicity

- Cytokine release syndrome
  - Sequelae of this sepsis like syndrome
  - Hemophagocytic lymphohistiocytosis (HLH)
- Neurotoxicity (immune effector cell-associated neurologic syndrome)
  - Most severe form cerebral edema, seizure, profound AMS
- Hypersensitivity reaction
- Tumor lysis syndrome

Acute CAR-T Toxicity continued…

- Persistent Cytopenia after T Cell Therapy
- Coagulopathy
  - DIC in setting of severe CRS
- B-cell aplasia and hypogammaglobulinemia (CD-19 specific)
- Infections
- Acute Kidney Injury/ Electrolyte Dyscrasias
- Cardiopulmonary toxicities
  - Arrhythmias, pulmonary edema
- Hemophagocytic lymphohistiocytosis (**HLH**)

AKI and Electrolyte Abnormalities After CAR-T Therapy

Setting & Participants

Case Series (2017-2019)

78 hospitalized patients in 2 cancer centers

Diffuse large B-cell lymphoma

Chimeric antigen receptor T-cell therapy

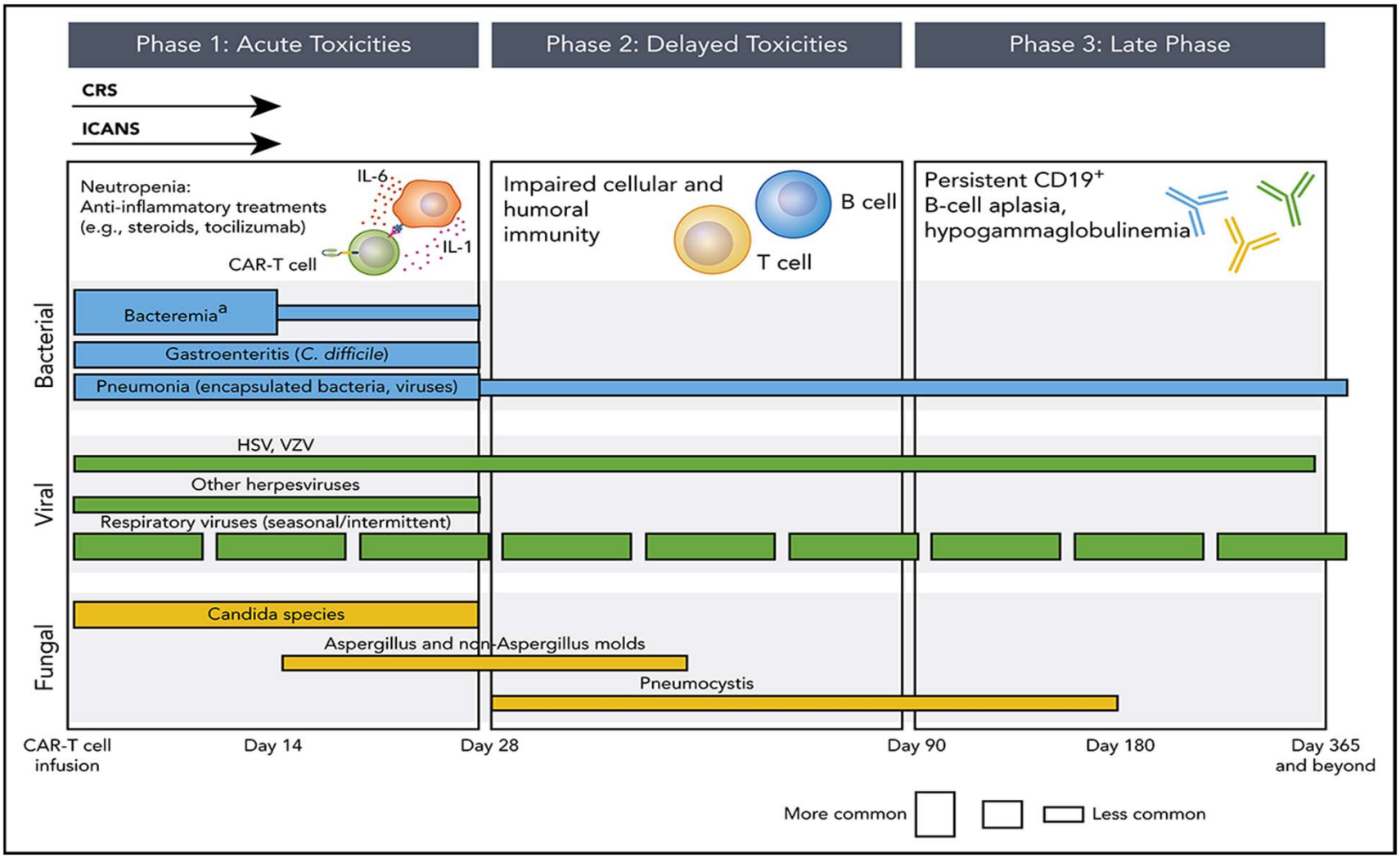
Findings

Acute kidney injury	19%
Cytokine release syndrome	85%
↓Na (<135 mEq/L)	75%
↓K (<3.5 mEq/L)	56%
↓PO_4 (<2.5 mg/dL)	51%

CONCLUSION: Cytokine release syndrome, AKI, hyponatremia, hypokalemia, and hypophosphatemia are common after CAR-T therapy

Shruti Gupta, Harish Seethapathy, Ian Strohbehn, et al (2020)
@AJKDonline | DOI: 10.1053/j.ajkd.2019.10.011

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES



Joshua A. Hill,Susan K. Seo, How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies, Blood, 2020,

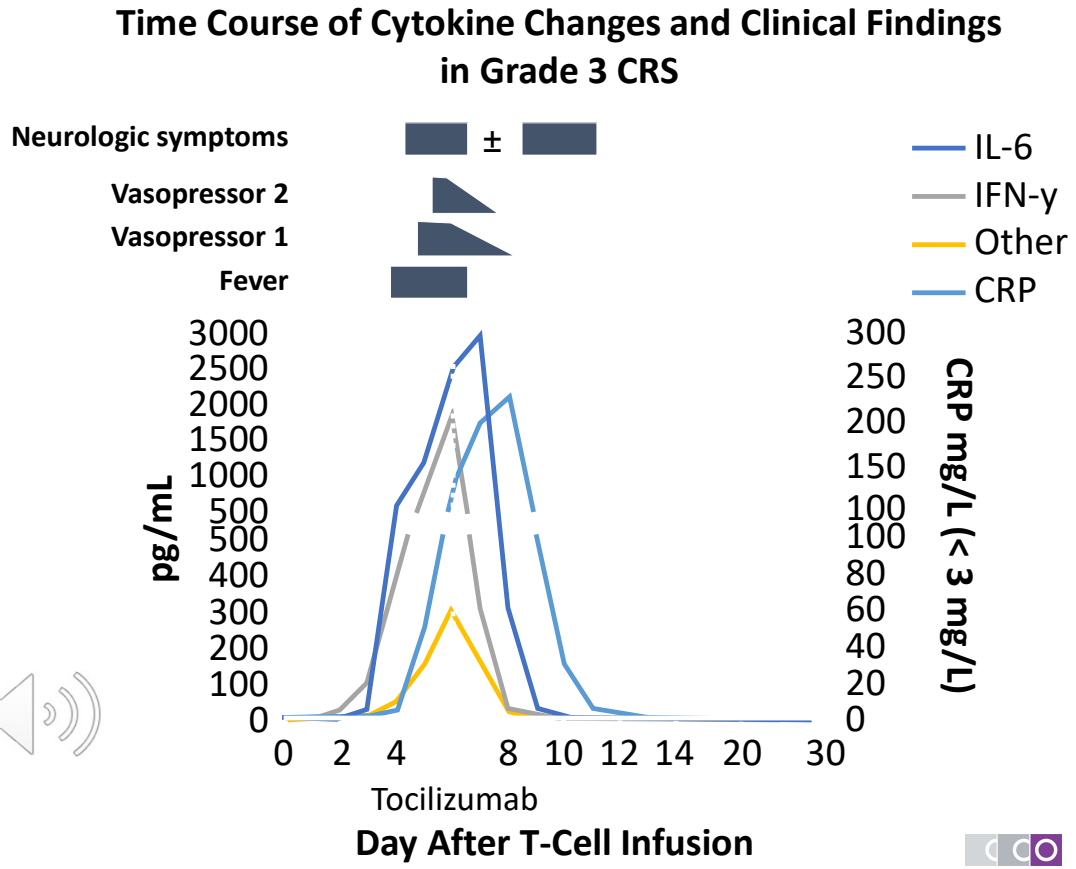
CRS

CRS ICANS Pathophysiology

- Monoclonal antibodies, bi-specific antibodies, anti-lymphocyte globulin, and haploidentical transplant
- Activation of CAR-T → release of effector cytokines such as interferon-y, tnf-a, and IL2 → activate monocyte/macrophage system and induce the production of broad inflammatory cytokines like IL1, IL6, IL10
- Inflammatory cytokine release triggers increased vascular permeability and altered blood brain barrier through endothelial activation

Cytokine-Release Syndrome (CRS)

- Typical onset 2-3 days, duration 7-8 days, ICANS typically follows
- Systemic inflammatory response that occurs as CAR T-cells activate and expand
- High levels of CRP, ferritin, IL-6, IL-10
- Flu-like symptoms with fever
- Can progress to life threatening hypotension, hypoxia, and death
- High disease burden associated with more severe CRS



Lee. Blood. 2014;124:188.

Slide credit: clinicaloptions.com

CRS Toxicities by Organ System

Neurologic

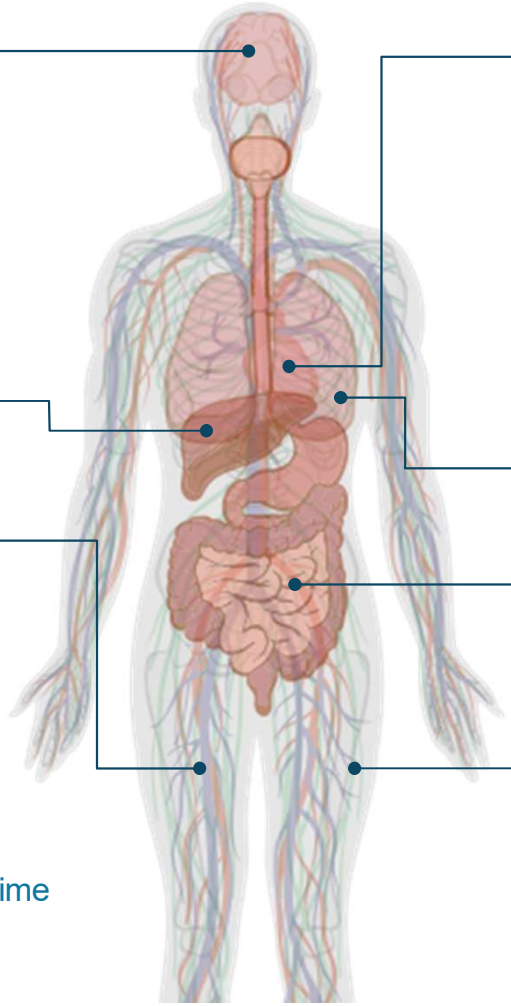
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial Nerve palsy
- Seizures

Hepatic

- Transaminitis
- Hyperbilirubinemia

Hematologic

- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile Neutropenia
- Lymphooenia
- B-Cell Aplasia
- Elevated D-Dimer
- Hypofibrinogenemia
- Dissembled Intravascular Coagulation
- Hemophagocytic Lymphohisticyclosis
- Prolonged Prothrombin time
- Prolonged Activated Partial Thromboplastic time



Cardiovascular

- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fracture
- Troponinemia
- QY prolongation

Pulmonary

- Tachypnea
- Hypoxia

Gastrointestinal

- Nausea
- Diarrhea
- Emesis

Musculoskeletal

- Myalgias
- Weakness
- Elevated creatine kinase

Constitutional

- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Aethralgais

Renal

- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

blood

ASTCT Guidelines for Grading of Cytokine Release Syndrome

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 38°C	Temp ≥ 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloptions.com

ICANS

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- Symptoms
  - Delirium
  - Encephalopathy
  - Aphasia
  - Lethargy
  - Difficulty concentrating
  - Agitation
  - Tremor
  - Seizures
  - Cerebral edema
  - (Headache)

"…an awake patient who is mute and does not respond verbally or physically to an examiner"

- Typical onset 4-6 days, typical duration 14-17 days; can occur in the presence of absence of systemic CRS (usually after)
- Pathophysiology
  - Endothelial activation → blood–brain barrier disruption
  - Elevated levels of the excitatory NMDA receptor agonists?
  - Proinflammatory cytokines
  - Activated T- and myeloid cells

Gust. Cancer Discov. 2017;7:1404. Cancer Discov. 2018;8:4. Lee. Biol Blood Marrow Transplant. 2019;25:625.

Slide credit: clinicaloptions.com

Encephalopathy Assessment Tools for Grading of ICANS

ICE		
Orientation:	Orientation to year, month, city, hospital	4 points
Naming:	Ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following Commands:	Ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing:	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1 point
Attention:	Ability to count backwards from 100 by 10	1 point

ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (pt 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 nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 mins) 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

*See next slide; an ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Differential Diagnosis for ICANS

- Electrolyte abnormalities
- Infection/sepsis
- Cytotoxic drugs
- Anti seizure drugs
- Hepatic failure
- Delirium
- CRS
- Progression of disease

Treatment of CRS and ICANS

Initial Toxicity Mgmt and Prevention

- TLS prevention and mgmt.
- Anti-infective ppx
  - Viral, fungal, bacterial?
- Lab monitoring
  - Crp, ferritin, IL6
  - TLS labs if needed
  - Coagulopathy D Dimer, PT/PTT, fibrinogen
- Avoid G-CSF for neutropenia, at least in the beginning
- Seizure ppx, baseline neurology assessment
- Frequent vital sign and neuro SCAN check

Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care	Supportive care	Supportive care
2	Tocilizumab	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)
3	Tocilizumab	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management. 2017. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Slide credit: clinicaloptions.com

CRS, ICANS treatments

- Tocilizumab
- Steroids
- Anakinra
- Siltuximab
- T Cell destruction (ATG, cyclophosphamide, Suicide gene)
- Cytokine removal

Which of the following medications should be used initially to treat grade 2 CRS?

- Siltuximab
- Tocilizumab
- 1 gram Methylprednisolone
- Pembrolizumab

Which of the following would be seen in grade 1 ICANS?

- Hemiparesis
- Aphasia
- Seizure
- Difficult to arouse/sedate

Which of the following is NOT an adverse effect of ipilimumab?

- Dermatitis
- Thrombocytosis
- Colitis
- Hypophysitis

- A 58 y/o F w/ relapsed refractory diffuse large B cell lymphoma received Axicabtagene ciloleucel 3 days ago. She was conditioned w/ fludarabine and cyclophosphamide for lymphodepletion. Her course has been complicated by mild nausea. She reports chills and fatigue when she wakes up.

- AM VS: 78/44 mmHg, 111 bpm, 101.9F oral temperature, 24 rpm, and room air SpO2 of 88%. She is placed on a 2L nasal cannula and improves to 93%.

- PE: + ill appearing, L/S w/ bilateral crackles at the base, PICC site w/o erythema, purulence, tenderness.

- LABS: CBC 1.2/10/188 ANC 1.2 BMP unremarkable.

- WHAT DIAGNOSTIC STUDIES? CRS LAB MARKERS, BLOOD/URINE CX, CXR, INTRANASAL INFECTION PCR, URINE STREP/LEGION, FUNGAL BLOOD MARKERS?
- DIFFERENTIAL DIAGNOSIS? CRS grade 2 vs Infection/sepsis
- WHAT TREATMENT ? ABX (vanc/cefepime), TOCILIZUMAB? STEROIDS?