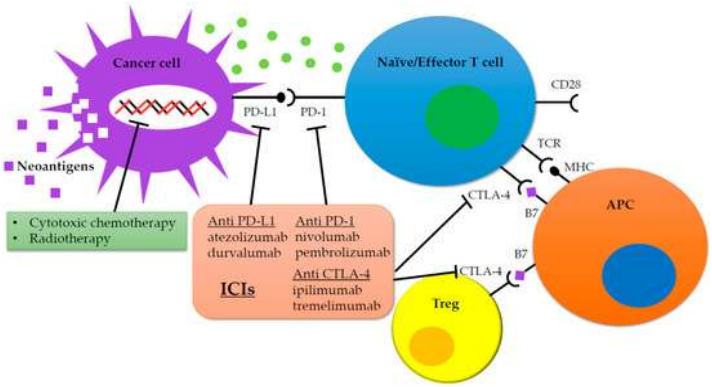
Toxicity Management

Brigett Brandjes PA-C
Marian Dam DNP, APRN
Department of Blood & Marrow Transplant and Cellular Immunotherapy
Moffitt Cancer Center

Disclosures

- No Disclosures
- I will be discussing non-FDA approved indications during my presentation.

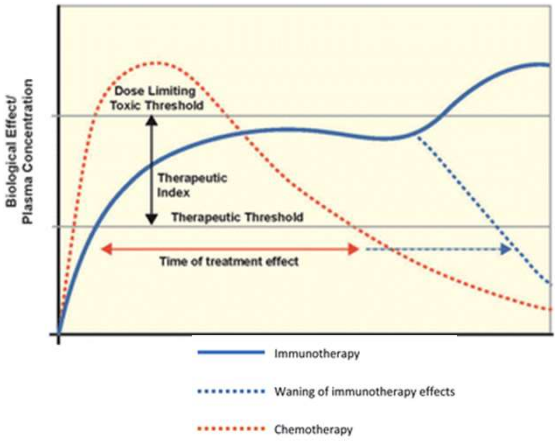
Checkpoint inhibitors



J. Clin. Med. **2020**, *9*(5), 1362

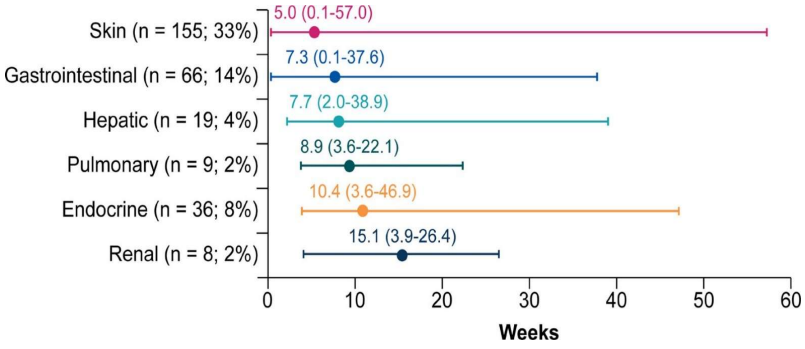
Immune-related adverse events (irAEs)

- Immune checkpoint inhibitor (ICI) toxicities often have delayed onset and prolonged duration relative to chemotherapy toxicity
- Toxicities result from non-specific activation of the immune system and can mimic a number of other medical conditions



Puzanov and Diab, JITC 2017

Onset of irAEs



- Can be days to months after therapy initiation
- May occur even after treatment is discontinued
- Important to identify patients who are currently OR previously on ICI treatment

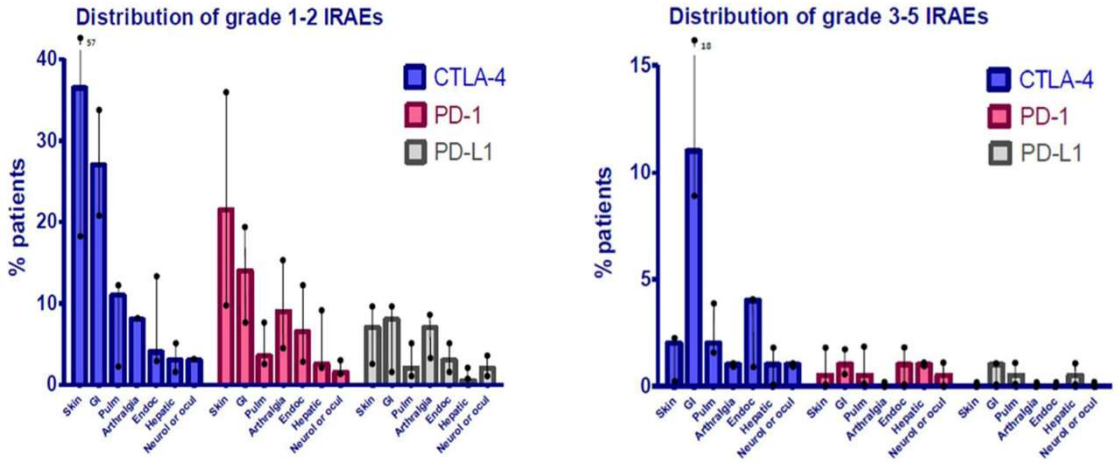
Pallin, Acad Emerg Med 2018
Puzanov and Diab, JITC 2017

Incidence of irAEs

- Overall incidence of all-grade irAEs with single-agent ICI reported as 15-90% in studies
- CTLA-4 inhibitor (ipilimumab): dose-dependent toxicities
  - Any grade toxicity ≤ 75% (**Grade 3+: ≤ 43%**)
- PD-1/PD-L1 inhibitors: toxicities less dose-dependent
  - Any grade toxicity ≤ 30% (**Grade 3+: ≤ 20%**)
- Life-threatening irAEs are rare but treatment-related deaths reported in up to 2% of clinical trial patients

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Severity of irAEs by ICI



Puzanov and Diab, JITC 2017

Common irAEs with ICI's

- Dermatologic: maculopapular rash, dermatitis, pruritis
- Gastrointestinal: diarrhea, colitis, hepatitis, gastritis
- Rheumatologic: arthralgias, myositis, sicca symptoms
- Pulmonary: pneumonitis, sarcoidosis
- Endocrine: thyroid dysfunction, hypophysitis

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Uncommon irAEs with ICI's

Cardiovascular:
Myocarditis, pericarditis, arrhythmias

Renal:
Interstitial nephritis, granulomatous nephritis

Endocrine:
Adrenal insufficiency, pancreatitis, type 1 diabetes mellitus

Hematologic:
Hemolytic anemia, red cell aplasia, neutropenia, thrombocytopenia

Neurologic:
Myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathies, transverse myelitis

Ophthalmologic:
Uveitis, episcleritis, conjunctivitis

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Pre-treatment screening

- Patient History
  - Autoimmune, infectious, endocrine, organ-specific diseases
  - Baseline bowel habits
- Dermatologic
  - Full skin and mucosal exam
- Pulmonary
  - Baseline O_2 saturation
- Cardiovascular
  - ECG
  - Troponin I or T
- Blood tests
  - CBC with diff
  - CMP
  - TSH and free T4
  - HbA1c
  - Total CK
  - Fasting lipid profile
  - Infectious disease screen:
    - Hepatitis serologies
    - CMV antibody
    - HIV antibody and antigen (p24)
    - TB testing (T-spot, quantiferon gold)

Pazanov & Diab, JITC 2017.

Additional screening for high-risk patients

- Endocrine tests
  - 8 am cortisol and ACTH
- Cardiac tests
  - Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
- Pulmonary tests
  - PFTs
  - 6MWT

Pazanov & Diab, JITC 2017.

Approach to Treatment

- Treatment is guided by grading of specific toxicity
- Resources for grading:
  - SITC Toxicity Management Working Group
  - Common Terminology Criteria for Adverse Events
  - National Comprehensive Cancer Network
  - American Society of Clinical Oncology
- 1st line for **MOST** irAEs is systemic high-dose corticosteroids
  - Endocrine toxicities managed with hormone replacement
  - Some grade 1-2 irAEs may respond to topical steroids (dermatologic, ophthalmologic)
- OTC drugs may not be appropriate for managing symptoms
  - i.e. loperamide for colitis may result in bowel perforation

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
1	Usually not indicated	Continue immunotherapy
2	• Start **prednisone 0.5-1 mg/kg/day** (or equivalent dose of IV methylprednisolone) • If no improvement in 2-3 days, **increase dose** to 2 mg/kg/day • Once improved to ≤grade 1, start **4-6 week steroid taper**	• **Hold immunotherapy** during corticosteroid use • **Continue immunotherapy** once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis

Pazanov & Diab, JITC 2017.

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	• Start **prednisone 1-2 mg/kg/day** (or equivalent dose of IV methylprednisolone) • If no improvement in 2–3 days, **ADD additional** immunosuppressant • Once improved to ≤ grade 1, start **4–6-week steroid taper**	• **Hold immunotherapy**; if symptoms do not improve in 4–6 weeks, **discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4		• **Discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PJP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

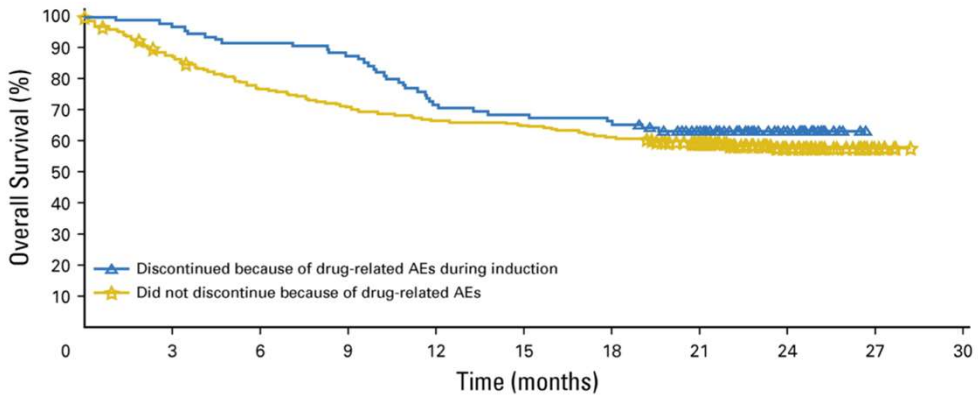
Pazanov & Diab, JITC 2017.

Additional Immunosuppressive Agents

- Infliximab: anti-TNF-α mAb
  - Hepatotoxic so should NOT be used for immune-mediated hepatitis
  - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
  - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: α4β7 integrin mAb
  - **Selective GI immunosuppression** → inhibits migration of T cells across endothelium into inflamed GI tissues
  - Dose: 300 mg; repeat dose at 2 and 6 weeks
- Others: mycophenolate, IVIG, tacrolimus

Abu-Sbeih H. JITC. 2018 Dec 5;6(1):142.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

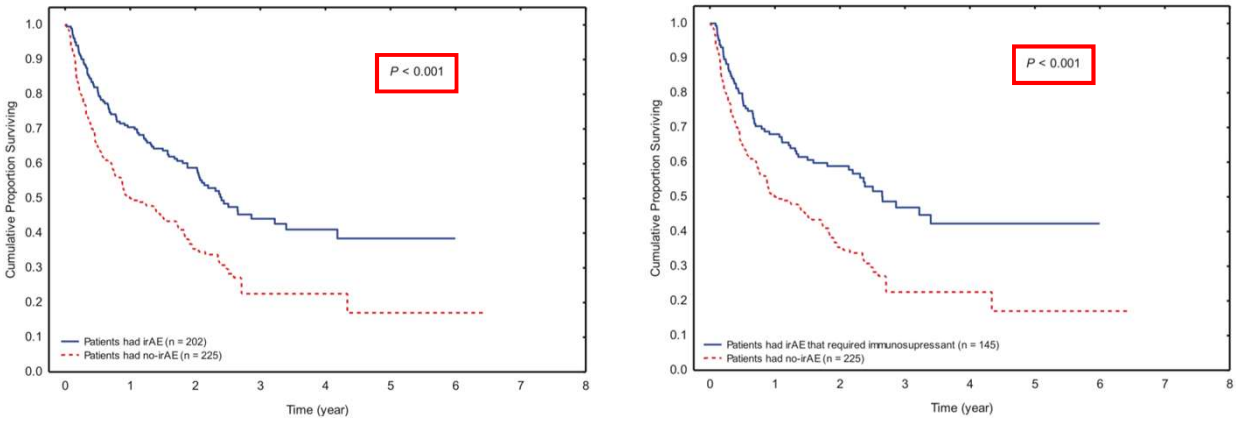
Effect of irAEs on patient outcomes



No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

Schadendorf D. J Clin Oncol 2017 Dec; 35(35):3807-3814.

Autoimmunity as prognostic marker?



Based on retrospective data, patients who experience irAEs (regardless of needing treatment) may have better outcomes compared to patients who do not experience irAEs

Abu-Sbeih, J Immunoth Prec Oncol 2018.

Patients with autoimmune disorders

- Ipilimumab in melanoma patients
  - 29% experienced flare of pre-existing disorder; 29% experienced new irAEs
  - 56% experienced no flare OR additional irAEs
- PD-1 in melanoma patients
  - 38% experienced flare; 29% experienced new irAEs
  - Lower response rates in patients who remained on immunosuppressive treatment (15% vs 44%)
- Efficacy appears similar for patients with autoimmune disorders compared to those without

Kahler KC. Cancer Immunol Immunother. 2018.

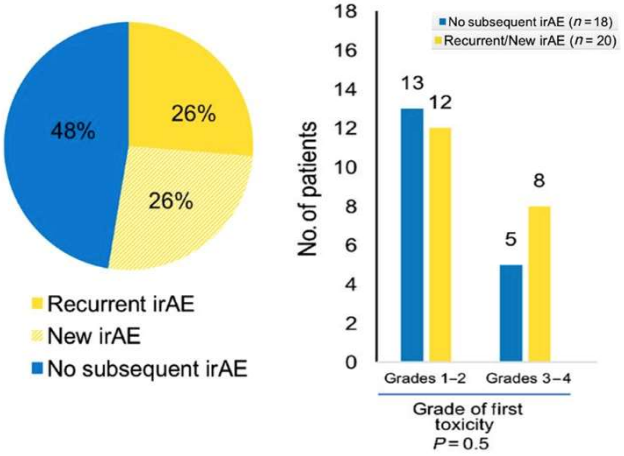
ICI use in SOT or SCT

- Patients who relapse after allogeneic SCT:
  - Ipilimumab: 32% response (10 mg/kg); 14% GVHD; 21% irAEs
  - Anti-PD-1: 77% response; 26% died due to new-onset GVHD
- Solid organ data is limited; most is in renal SOT patients
  - One retrospective study (n=39) reported graft loss in 81% and death in 46%
  - Also reported rapid time to rejection with median onset of 21 days
- PD-1 pathway appears to be more critical in allograft immune tolerance compared to CTLA-4 pathway

Davids MS. NEJM 2016.
Haverkos BM. Blood 2017.
Abdel-Wahab. JITC 2019.

Re-challenging with ICI after irAEs

- Patients should not be re-challenged until irAE resolved to grade ≤1
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4 ± anti-PD-1 likely safe
- Caution in re-challenging with same ICI in patients who previously had grade 3-4 irAEs



Santini FC. Cancer Immunol Res 2018.

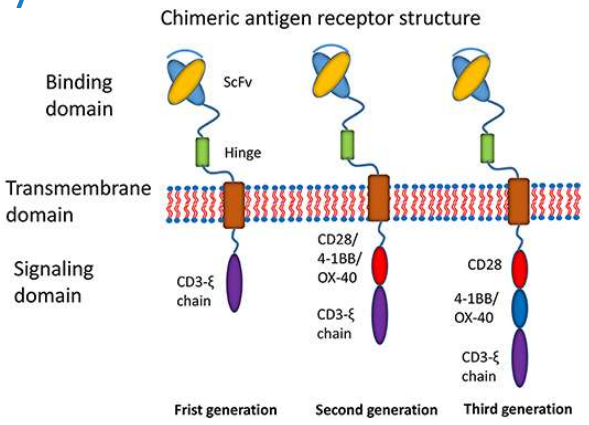
CAR-T Cell Therapy

What is a CAR?

- Chimeric Antigen Receptor
  - "living drug"

What is CAR-T Cell Therapy?

- Personalized targeted treatment
  - T cells are expanded ex vivo
  - CARs transduced using viral vector
  - After infusion cells proliferate
  - Degree of expansion in vivo associates with efficacy



https://www.frontiersin.org/articles/10.3389/fimmu.2019.00456/full

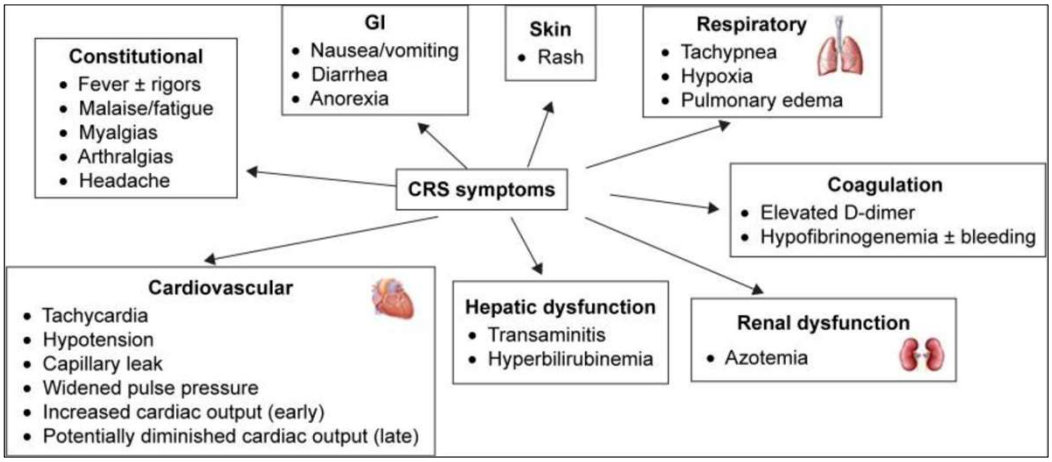
Hay KA et al. Drugs 2017.Mar

CAR T-cell Related Toxicities

Less Common	Anaphylaxis, B cell aplasia and hypogammaglobulinemia
	Hemophagocytic Lymphohistiocytosis/ Macrophage Activation Syndrome (HLH/MAS)
More Common	Immune effector cell associated neurotoxicity syndrome (ICANS)
	Cytokine release syndrome (CRS)

NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Cytokine Release Syndrome



Riegler LL. Ther Clin Risk Manag 2019.

Cytokine Release Syndrome

- Occurs in ~70% of patients; severe = 12-47%
  - Median onset 2-3 days after infusion, typical duration 7-8 days
- Multiple grading systems exist (MSKCC, CARTox, ASTCT)
  - Hypotension and hypoxia are main drivers of CRS severity
- Tocilizumab approved for CRS treatment (blocks IL-6R)
  - Dose for patients >30 kg: 8 mg/kg (up to 800 mg/dose)
  - May be repeated every 8 hours up to 4 doses
- Consider adding dexamethasone 10 mg q6h for grade 3-4 CRS **and/or** refractory to tocilizumab

Lee DW. BBMT 2019.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

ASTCT CRS Consensus Guidelines

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	T_m ≥100.4°F	T_m ≥100.4°F	T_m ≥100.4°F	T_m ≥100.4°F
With either:				
Hypotension	None	Responsive to fluids	Requiring 1 vasopressor (w/ or w/o vasopressin)	Requiring multiple vasopressor (excluding vasopressin)
And/or **Hypoxia**	None	Low-flow nasal cannula or blow-by	High-flow nasal canula, facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (CPAP, BiPAP Intubation and mechanical ventilation)

*Fever not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as 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.
+ Low-flow nasal cannula is defined as oxygen delivered at ≤ 6L/minute. High-flow nasal cannula is defined as oxygen delivered at >6L/minute

Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. pii: S1083-8791(18)31691-4.

Neurotoxicity

- Known as CAR-T Related Encephalopathy Syndrome (CRES) or most recently IEC-associated neurotoxicity syndrome (ICANS)
- Occurs in 20-64% of patients, ≥ grade 3 in 11-42%
  - Onset 4-5 days after infusion, typical duration 5-12 days
- Common symptoms include encephalopathy, headache, delirium, anxiety, tremor, aphasia
  - Severe neurotoxicity: seizures, cerebral edema, hemi/paraparesis
- Diagnosis usually based on clinical symptoms
  - MRI/CT often negative although ~30% will have abnormal MRI
- Also has multiple grading systems which guide treatment
  - Usually includes early use of high-dose steroids (dexamethasone 10 mg IV q6h)

Wang Z. Biomark Res. 2018.
Hunter BD. J Natl Cancer Inst. 2019.

ASTCT ICANS Consensus Guidelines

	Grade 1	Grade 2	Grade 3	Grade 4
Immune Effector Cell-Associated Encephalopathy (ICE) Score *	7-9	3-6	0-2	0 (Patient unarousable sand incapable of performing ICE test)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	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 resolved rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life threatening prolonged seizure (>5min) or electrical seizures without return to baseline in between
Elevated intracranial pressure/cerebral edema	N/A	N/A	Focal or local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial never VI palsy, papilledema, or Cushing's triad
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. pii: S1083-8791(18)31691-4.

CRS and Neurotoxicity

- Overlapping toxicities from excessive immune activation
- May occur together or exclusive of one another
- However, they do have distinct timing and responses to treatment
- Risk factors for both include:
  - High disease burden
  - Higher infused CAR-T cell dose
  - High intensity lymphodepletion regimen
  - Pre-existing endothelial activation
  - Severe thrombocytopenia

Santomasso BD. Cancer Discov 2018.
Wang Z. Biomark Res. 2018.

HLH/MAS

- Inflammatory syndrome caused by hyperactivation of macrophages and lymphocytes
- Rare; frequency reported to be as low as ~1%
- Treatment includes anti-IL-6 and corticosteroid therapy
- If no improvement after 48 hours, consider adding etoposide for additional immunosuppression
  - Dose: 75-100 mg/m^2
  - May be repeated after 4-7 days

Box 5 | Diagnostic criteria for CAR-T-cell-related HLH/MAS

A patient might have HLH/MAS if he/she had a peak serum ferritin level of >10,000 ng/ml during the cytokine-release syndrome phase of CAR-T-cell therapy (typically the first 5 days after cell infusion) and subsequently developed any two of the following:

- Grade ≥3 increase in serum bilirubin, aspartate aminotransferase, or alanine aminotransferase levels*
- Grade ≥3 oliguria or increase in serum creatinine levels*
- Grade ≥3 pulmonary oedema*
- Presence of haemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

Titov A. Cell Death Dis. 2018.
Neelapu SS. Nat Rev Clin Oncol. 2018.

The importance of education

- Many immune-related adverse events can present in similar ways to other disease states, but the treatment of them is very different
  - Patient and healthcare education are key
- Patients may not go back to their oncologist for treatment of irAEs and need to identify themselves as immunotherapy recipients
  - Emergency departments and primary care physicians need to recognize and know how to manage irAEs
- Reassure patients that most irAEs will likely resolve over time

Case Study 1

48 y.o Male

- Hx of HL, nodular sclerosis type
- ABVD X4 cycles, ICE X 3 cycles
- Autologous HSCT with BEAM conditioning 04/2012
- Panobinostat and Revlimid then brentuximab X 3 cycles, bendamustine X 2 cycles in
- Allogeneic mismatched donor tx 05/2014 with Fludarabine/Busulfan

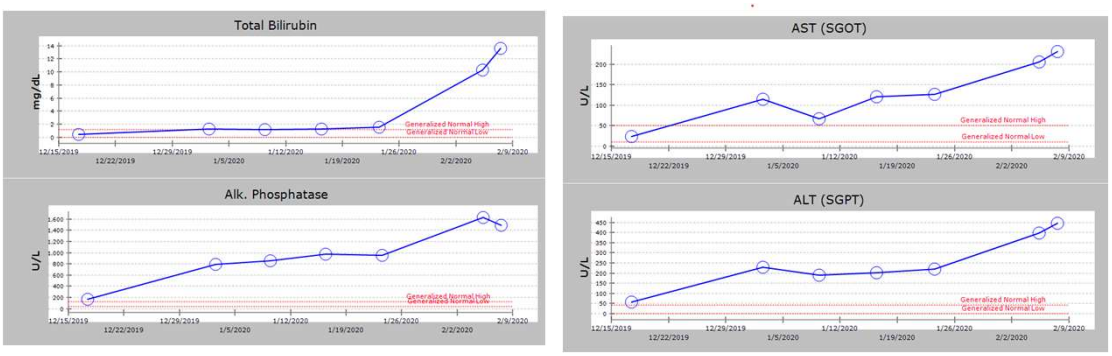
Current status

- Progression of disease with lymphadenopathy, anemia, and constitutional symptoms in 10/2019.
- Hx of chronic GVHD (ocular, oral, skin)
- Started on treatment with **Nivolumab** 1mg/kg q 28 days on 11/8/19. S/p cycle 3 on 1/3/20 (also received cytoxan x 1 dose on 1/3/20).

Initial presentation

- Here for routine follow up post transplant relapse on nivolumab therapy with his of GVHD and mild transaminases. Appears jaundice on exam. Denies any new medications
- Current medications: tacrolimus, prednisone, gabapentin, losartan
- Laboratory findings reveal mild anemia and and AST 210, ALT 460, ALP 1000
- Vitals: Temp 98.8F, BP 130/72, HR 84, RR 14, 99% SpO2 on RA, 79kg

Initial presentation



Case Study 1

- Conjugated bilirubin
  - direct 15, indirect 4
- Viral studies
  - Hepatitis (HAV, HBV,HBV) screen negative
  - CMV and EBV PCR neg
- Ultrasound doppler of liver
  - Normal hepatic veins and artery, sluggish flow. No ascites
- Synthetic function
  - Coag panel normal, Platelets 152K, albumin 2.8, Total protein 6.0

Treatment Summary

- What grade and type of toxicity did the patient have?
- Grade 1 hepatitis
- Grade 2 hepatitis
- Grade 3 hepatitis
- Grade 4 hepatitis

- Steroids increased to 2mg/kg
  - Consider IV
  - Add PPI and or H2RA
- No improvement after 72 hours
  - Tacrolimus increased and added MMF 1gm BID
- Sulfamethazole-trimethoprim SS daily
- Consider hospitalization and close monitoring
  - If enzymes improve, taper over 4 weeks
  - Consider liver biopsy if worsening

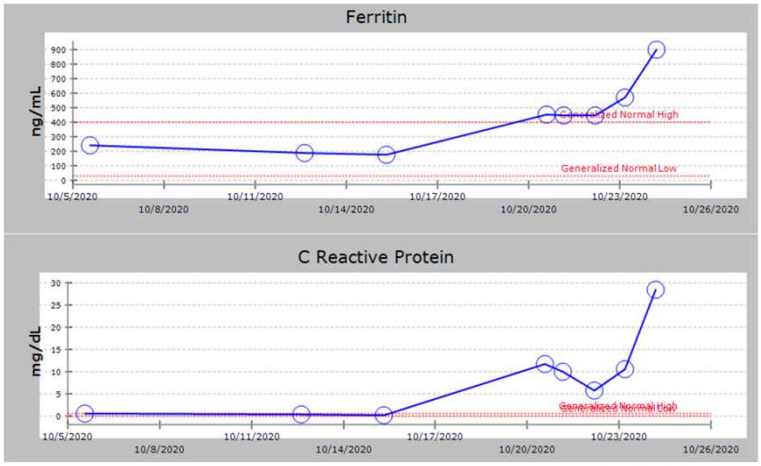
Case Study 2

A 51-year-old female with relapsed refractory Stage IV DLBCL. Prior treatments include RCHOP x 6, RICE, RDHAP, and Auto HSCT with progressive disease. She received lymphodepletion chemotherapy and was admitted to the hospital followed by CAR T infusion

Day 0 (Baseline) Vitals: BP 122/82, HR 77, RR 14, Temp 98.4F, 99% on RA

Day +4 Vitals: BP 90/40, HR 130, RR 18, Temp 103.2F, 99% on RA

Case Study 2



Case Study 2

What Grade CRS is the patient experiencing and what is your next step in management?

A. Grade 1 CRS + initiate infectious work up along with antibiotics
B. Grade 2 CRS + tocilizumab
C. Grade 2 CRS + tocilizumab + initiate infectious workup
D. Do nothing and monitor the patient closely

Case Study 2

Assessment:

- Grade 2 CRS
  - Fevers + Hypotension

Plan:

- Tocilizumab 800mg IV x 1
  - Can repeat the dose in 8 hours if needed (Max 4 doses)
  - Consider dexamethasone if no improvement

Key Points:

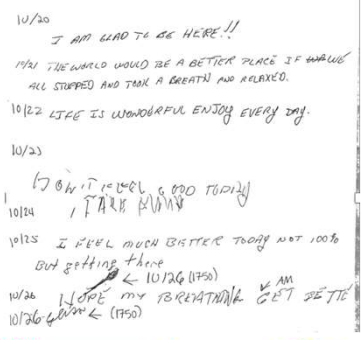
- Frequent assessment is crucial
- Don't forget to rule out infection
- Timely management in order to avoid further organ toxicities
- After treating with Tocilizumab (or anti cytokine therapy) fevers may not re-occur
  - Grading will be assessed by hypoxia/hypotension

Case Study 2

Day+7 you are notified by the RN the patient is somnolent though awakens to voice, confused, and agitated. Her ICE score is 6/10. She has no focal neuro deficits and PE is wnl.

What grade ICANS is the patient experiencing?

A. Grade 1
B. Grade 2
C. Grade 3
D. Grade 4



Case Study 2

Workup:

- MRI brain no acute findings
- EEG noted diffuse slowing
- Lumbar puncture unrevealing

Assessment:

- Grade 2 ICANS

Plan:

- Dexamethasone 10mg IV Q 6 hrs + PPI

Key points:

- Continue with frequent neuro checks
- ~30% will have abnormal MRI/CT
  - Increased risk of poor outcome
- Taper steroids once ≤ Gr 1
  - Most guidelines suggest tapering Q72 hrs

Additional Resources