



**A Whole New World:
A Case-Based Approach to Managing
CAR T-Cell Therapy and Immunotherapy Toxicities**

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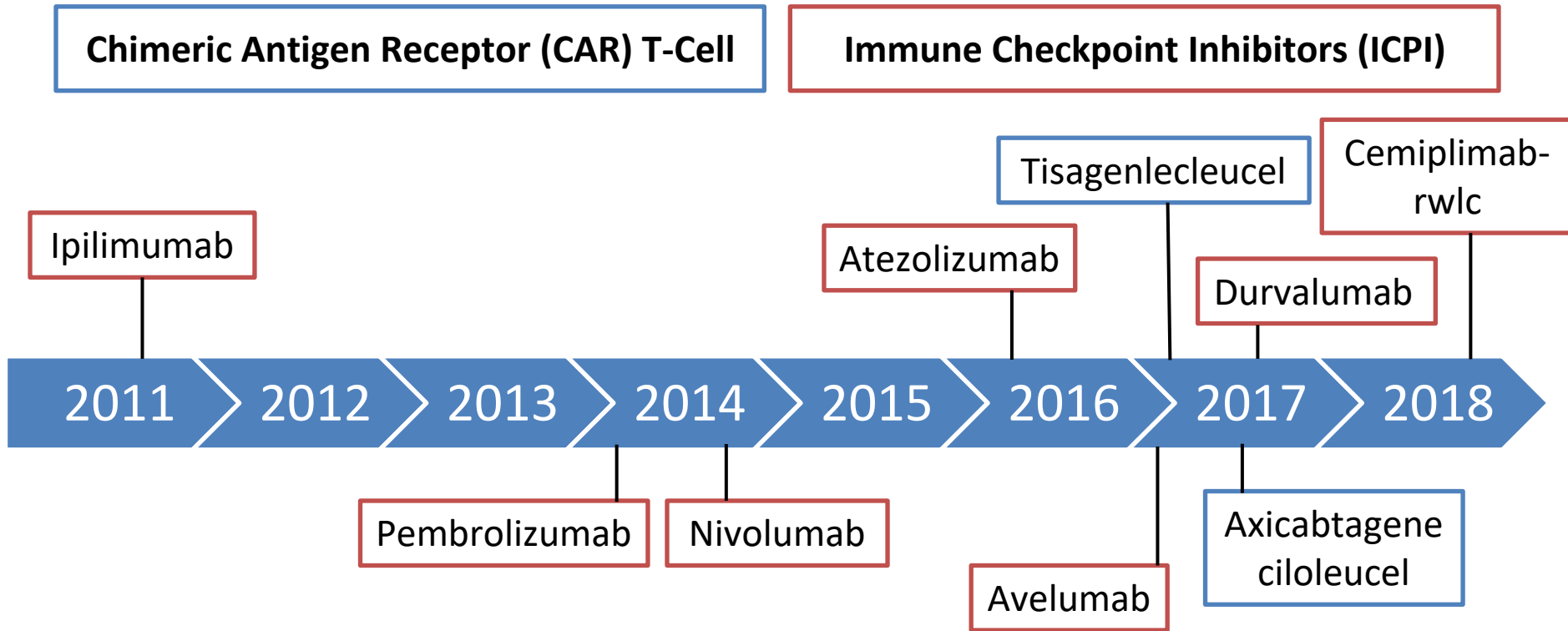
Disclosures

- **Larry W. Buie:** Heron: Advisory Board; Pfizer: Advisory Board
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Learning Objectives

- Interpret existing literature on chimeric antigen receptor (CAR) T-cell therapy immunotherapy management.
- Design therapeutic plans for managing CAR T-cell therapy and immunotherapy.
- Develop management guidelines to standardize treatment approaches.

A Whole New World



FDA-Approved CAR T-Cell Therapies

Name	Target
Tisagenlecleucel (Kymriah®)	CD-19
Axicabtagene ciloleucel (Yescarta®)	CD-19

FDA-Approved Immune Checkpoint Inhibitors

Name	Target
Ipilimumab (Yervoy®)	CTLA-4
Nivolumab (Opdivo®)	PD-1
Pembrolizumab (Keytruda®)	PD-1
Atezolizumab (Tecentriq®)	PD-L1
Avelumab (Bavencio®)	PD-L1
Durvalumab (Imfinzi®)	PD-L1
Cemiplimab-rwlc (Libtayo®)	PD-1

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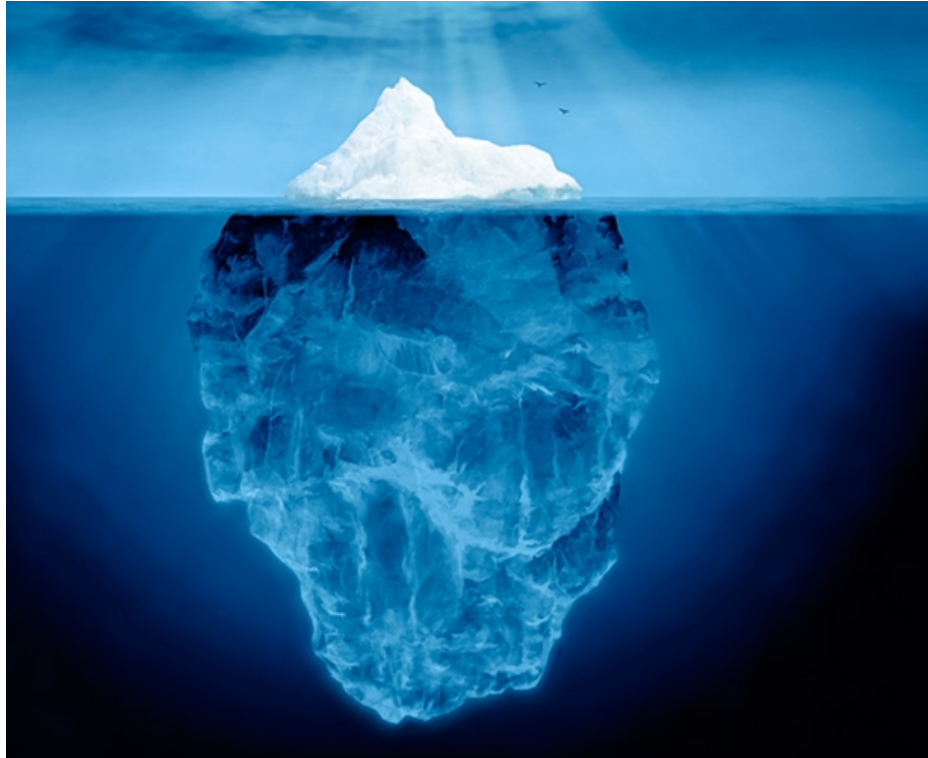
Efficacy

Safety

Financial

Growth

Immuno-Oncology



← What we know?

← What do we not know?

A Whole New World

CAR T-Cell Toxicities

- Supportive care requirements
- REMS program
- Monitoring
- Early identification

ICPI Toxicities

- Patient education
- Consistent monitoring
- Early identification
- Management of toxicities

Pharmacist Involvement

CAR-T Cell Therapy Toxicities

A Lesson From History: TGN1412

- CD28 superagonist monoclonal antibody
- 6 subjects without malignant disease
- Symptoms within 1 hour of infusion
 - Peak cytokine levels (TNF α , INF γ , IL-1 β , IL-2, IL-6, IL-8 and IL-10)
 - Initial symptoms: headache, nausea/vomiting, diarrhea, pyrexia
 - within 24 hours, renal failure, DIC and respiratory distress
- Treatment with corticosteroids, ranitidine, chlorpheniramine
- Cytokine levels returned to normal within 2 days

Death from CAR T-Cell Therapy

Study	Malignancy	CAR T-Cell	Day of Death	Cause of Death
Morgan 2010	Colon Cancer	HER2-28-ζ	5	ARDS
Brentjens 2010	CLL	CD19-28-ζ	2	CRS
Frey 2014	B-ALL	CD19-41BB-ζ Tisagenlecleucel (CTL019)	5 15 15	CRS (+Influenza) CRS (+Sepsis) CRS (+Sepsis)
Kochenderfer 2015	PMBCL	CD19-28-ζ	16	Cardiac arrest
Chong 2016	FL	CD19-41BB-ζ		Encephalitis
Neelapu (Zuma-1)	DLBCL	CD19-28-ζ Axicabtagene ciloleucel (KTE- C19)		HLH

Death from CAR T-Cell Therapy

Study	Malignancy	CAR T-Cell	Day of Death	Cause of Death
Locke 20116 (Zuma-1)	NHL	CD19-28-ζ		Cardiac arrest
Turtle 2016	B-ALL	CD19-41BB-ζ	3 122	CRS Neurotoxicity
Turtle 2016	NHL	CD19-41BB-ζ	30 13	CRS (+GI Bleed) Neurotoxicity (+CNS Bleed)
Rocket 2017	B-ALL	CD19-28-ζ (JCAR015)		Cerebral edema X 5
Zuma-1 (2017)	NHL	CD19-28-ζ		Cerebral edema
Turtle	CLL	CD19-41BB-ζ	11	Cerebral edema

CAR T-Cell Associated Toxicity

- Autoimmune
 - On-target, off-tumor
 - Tumor associated antigen expressed on non-malignant tissue
- Cytokine-associated
 - Lymphoid and myeloid activation
 - Release of cytokines
 - Non-antigen specific

Meet the Patient

- 30 year old male with Ph- ALL dx April 2015
 - HyperCVAD x 8 cycles → complete response (CR) 1
 - POMP maintenance, relapsed April 2016
 - CALGB 10403 → CR 2 with minimal residual disease (MRD) +
 - Blinatumomab initiated 1/2017
 - Bone marrow biopsy 3/2018
 - Revealed relapse with 30% blasts → T cells collected
 - CAR T-cell conditioning 5/1/2018
 - Cyclophosphamide and fludarabine
 - CAR T-cell infusion with no immediate adverse events on 5/6/2018

Meet the Patient

- 5/7/18 febrile and tachycardic
 - Empiric broad spectrum antimicrobials
 - Antipyretics
 - Negative workup for infection
- 5/8/18 hypotension and hypoxia
 - IV fluid bolus
 - Supplemental oxygen

ARS Question

DE has been transferred to the ICU for management of continued encephalopathy following CAR-T cell administration. Which of the following should be given to treat his cytokine release syndrome (CRS)?

- A. Infliximab
- B. Tocilizumab
- C. Adalimumab
- D. Muromonab

Assessing CAR T-Cell Toxicities

Determine CAR T-Cell Toxicity

CRS

- Fever
- Hypotension
- Hypoxia
- Organ Toxicity

Grade CRS

Manage according to grade of CRS

CRES

- CARTOX-10
- Seizure
- Increased ICP
- Motor Weakness

Grade CRES

Manage according to grade of CRES

HLH/MAS

- Ferritin
- Organ Toxicity
- Hemophagocytosis

Grade organ toxicity per CTCAE

Manage HLH/MAS according to algorithm

CRS Pathophysiology

- Most common toxicity of cellular immunotherapy
- Triggered by activation and expansion of T cells
- Complex pathophysiology
 - IL-2, soluble IL-2R α , INF γ , IL-6, soluble IL-6R, and GM-CSF
 - Monocyte and macrophage activation
 - Dendritic cell activation



Clinical Symptoms

Clinical Signs and Symptoms Associated with CRS

Organ System	Symptoms
Constitutional	Fever, rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia, bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty, aphasia, hallucinations, tremor, dysmetria, altered gait, seizure

CRS with CAR T-Cells

- High disease burden = increased antigen load = more toxicity
- Improved CAR constructs = more toxicity
 - Increased cytokine production
 - Increased T-cell activation and expansion
- Develops during the first week
- Peaks within 1-2 weeks of cell infusion
- Symptoms appear with maximal T-cell expansion
- May occur earlier with CD19-CD28- ζ (axicabtagene ciloleucel)

Grading of CRS

CRS Revised Grading System	
Grade	Toxicity
1	Symptoms are not life threatening and require symptomatic treatment only
2	Symptoms require and respond to moderate intervention Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention Oxygen requirement \geq 40% or Hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity
4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	Death

Management of CRS

CRS Grade	Symptom or Sign	Management
1	Fever	Antipyretics, IV fluids, empiric antibiotics, symptomatic management of organ toxicity Infection assessment Consider anti-IL-6 therapy
	Organ toxicity	
2	Hypotension	Fluid Bolus, vasopressors Anti-IL-6 therapy; repeat if needed
	Hypoxia	Supplemental oxygen Anti-IL-6 therapy as per hypotension
3	Hypotension	Fluids, anti-IL-6 therapy per CRS grade 2, vasopressors as needed Transfer to ICU; echocardiogram and hemodynamic monitoring Addition of corticosteroids
	Hypoxia	Supplemental oxygen including high flow oxygen delivery and positive pressure ventilation Anti-IL-6 therapy per CRS grade 2
4	Hypotension	Fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring per CRS grade 3 Addition of high dose corticosteroids
	Hypoxia	Mechanical ventilation Anti-IL-6 therapy per CRS 2

Biomarkers for CRS

- Barriers to biomarker utilization
 - Assays are not readily available
 - Severity of CRS is not predicted by cytokine levels
 - Panels need to measure multiple cytokines
- C-reactive protein (CRP)
 - Acute phase reactant
 - Produced in response to IL-6 production
 - Lag time is 1-2 days
 - Peak levels and fold increase in CRP may be predictive
- Ferritin is not predictive of CRS development but may indicate severity
- Hypofibrinogenemia

IL-6

- IL-6 is a mediator of toxicity in CRS
 - Strong positive correlation between IL-6 levels and severity of CRS
- It binds with gp130 (CD130) and IL-6 receptor (IL-6R, CD126))
- IL-6R is present on macrophages, neutrophils and hepatocytes
- When IL-6 levels are elevated, *trans*-signaling and activation of the proinflammatory IL-6 –mediated cascade occurs
- Leads to activation of JAK/STAT pathway signaling

Tocilizumab

- Humanized, immunoglobulin G1κ antihuman IL-6R mAB
 - Inhibits IL-6 binding to both cell-associated and soluble IL-6Rs
 - Inhibiting classical and proinflammatory *trans*-signaling
- FDA approved for CRS occurring after CAR T-cell therapy
- Side effects: transaminitis, thrombocytopenia, hyperlipidemia, and an increased risk of infection
- Effective treatment for CRS
 - Symptoms begin to clear within hours
 - Cytokines return to normal within 48 hours
- Dose: 4-8 mg/kg IV once and may be repeated
- Must keep 2 doses per patient available per REMS for approved CAR T-cell therapies

Tocilizumab-Refractory CRS

- Tocilizumab refractory CRS may emerge as a distinct pathophysiological entity
- All patients had ALL treated with anti-CD22 CAR T cells
- 10 subjects evaluated; 7 developed CRS
- One patient developed grade 4 CRS with manifestations of HLH that was unresponsive to tocilizumab
 - Higher IL-2 (35 pg/mL) versus median 6.1
 - GM-CSF level higher at 12 hours (28 pg/mL) versus median 1
 - No rise in IL-6
 - Ultimately had CR

HLH/MAS: A Complication of CAR T-Cells

- Constellation of symptoms
 - High fevers, hepatosplenomegaly, hepatic dysfunction, coagulopathy, hypofibrinogenemia and hyperferritinemia
- IL-2R, MCP-1 and MIP1B and other proinflammatory cytokine production
- Leads to immune activation and excessive inflammation
- Lymphocytic tissue infiltration
- Splenomegaly
- Hemophagocytosis present in bone marrow
- Multisystem organ failure may result
- Tocilizumab is treatment of choice
- Some may choose HLH directed treatment with etoposide

Other Alternatives for Prevention and Treatment of CRS

- Prophylactic tocilizumab?
- CAR T-cell dose refinement
- Siltuximab – binds IL-6
 - Full effect of immunosuppressives unknown
- In CAR-T treated mice, one week of ruxolitinib starting from day 1 of CAR-T infusion resulted in less severe CRS with attenuated inflammatory cytokines—no reductions in efficacy
- Ibrutinib with CART19 may enhance antitumor response and modulate T cell cytokine response , effectively reducing CRS
- Incorporation of suicide genes

Frey NV, Shaw PA, Hexner EO, et al. ASCO annual Meeting Abstract 7002. Presented June 4, 2016.

Park JH, Riviere I, Wang X, et al. ASCO Annual meeting. Abstract 7003. Presented June 4, 2016.

Ruella M, Kenderian SS, Shestova O, et al. ASH 58th Annual Meeting & Exposition; abstract 2159. Presented December 3, 2016.

Kenderian SS, Ruella M, Shestova O, et al. ASH 58th annual meeting & exposition; abstract 652. Presented December 5, 2016

Back to Patient DE

- 5/16/18 altered mental status
 - Head CT and EEG negative
- 5/17/18 persistent encephalopathy
 - Left arm weakness and facial droop
 - Transfer to ICU
 - MRI Brain negative
 - Dexamethasone 20 mg IV X 1

Assessing CAR T-Cell Toxicities

Determine CAR T-Cell Toxicity

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Grade organ toxicity per CTCAE

Manage HLH/MAS according to algorithm

CAR T-Cell-Related Encephalopathy Syndrome (CRES)

- Typically manifests as toxic encephalopathy
 - Earliest signs are diminished attention, language disturbance, impaired handwriting
 - Severe CRES is associated with seizures, mental obtundation, increased ICP, and cerebral edema
- May be biphasic
 - Phase I: typically within first 5 days
 - Fever and other CRS symptoms present
 - Typically shorter duration and lower grade
 - Responsive to anti-IL-6 therapy
 - Phase II: delayed neurotoxicity occurring during weeks 3-4 after CAR T-cell therapy
 - Longer duration and higher grade neurotoxicity
 - Anti-IL-6 therapy is not effective!

Pathophysiology of CRES

- Passive diffusion of cytokines into the brain
 - High serum levels of IL-6 and IL-15 associated with severe neurotoxicity
- Trafficking of T cells into the CNS
 - Presence of CAR T-cells in cerebrospinal fluid from patients with neurotoxicity
- Disruption of blood brain barrier
 - Elevated protein levels
- Secondary cortical irritation
 - Diffuse generalized slowing consistent with encephalopathy on EEG
 - Seizure activity
- MRI and CT scans are usually negative
 - Exceptions: cerebral edema

Grading of CRES

CRES grading system	
Grade	Toxicity
1	CARTOX-10 score of 7-9 (mild impairment)
2	CARTOX-10 score of 2-6 (moderate impairment)
3	CARTOX-10 score of 0-2 (severe impairment) Raised intracranial pressure with stage 1-2 papilledema or CSF opening pressure <20 mmHg Partial or non-convulsive seizures on EEG with response to benzodiazepine
4	Critical condition and/or obtunded Cannot perform CARTOX-10 assessment of tasks Stage 3-5 papilledema or CSF opening pressure \geq 20 mmHg Generalized seizures, convulsive or non-convulsive status epilepticus New motor weakness

Management of CRES

Grade	Management Recommendations
1	Supportive care, IV fluids Withhold oral intake Management of agitation Neurology consult: papilledema assessment, lumbar puncture, MRI, EEG If associated with CRS, consider anti-IL-6 therapy
2	Dexamethasone 10 mg IV q6h or methylprednisolone 1 mg/kg q12h if refractory to anti-IL-6 therapy, or for CRES without concurrent CRS Consider transfer to ICU
3	Transfer to ICU Corticosteroids, continue until grade 1 CRES then taper Acetazolamide
4	Consider mechanical ventilation Seizure management High dose corticosteroids Management of increased ICP and papilledema

ARS Question

DE continues to deteriorate and becomes obtunded in the ICU requiring mechanical ventilator support. He has no signs of CRS. Which of the following is the most appropriate treatment strategy?

- A. Ibrutinib 420 mg PO daily
- B. Tocilizumab 8 mg/kg X 1, repeat if necessary
- C. Adalimumab 40 mg SC every two weeks
- D. High dose steroids until CRES symptoms resolve to grade 1, then taper

Why are there no “Universal Guidelines”?

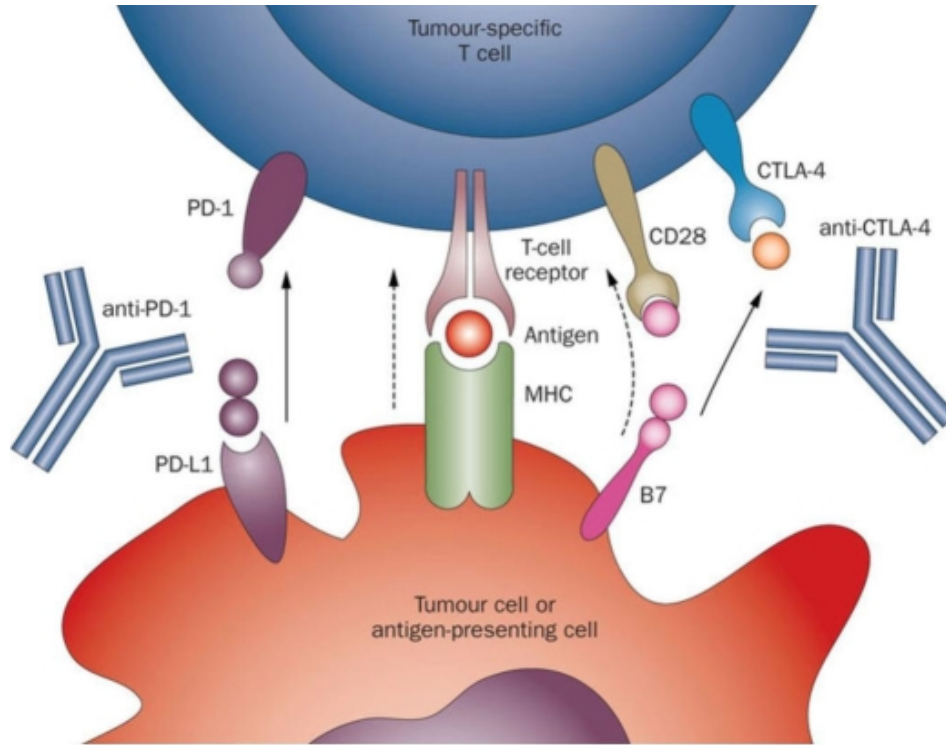
- Different CAR T-cell constructs
 - Different magnitude and timing of toxicity
- Different disease states
 - NHL
 - ALL
- Patient characteristics
 - Age
 - Comorbidities
 - Prior therapy
 - Cytokine response
- Variability in biomarker utilization/reliability
- Inpatient versus outpatient
- Dose, timing, and choice of corticosteroids
- Dose, timing, and choice of anti-IL6 blockade

CAR T-Cell KEY TAKEAWAYS

- 1) *CRS and CRES should be quickly identified in patients receiving CAR T-cells.*
- 2) *Appropriate therapy for CRS and CRES may include anti-IL-6 directed therapy (tocilizumab), corticosteroids, or a combination of the two if CRES with concomitant CRS.*
- 3) *A multidisciplinary approach is required to manage patients that develop CRS or CRES.*

ICPI Toxicity: Hepatotoxicity

Immune Checkpoint Inhibitors: Mechanism of Action



CTLA-4 – cytotoxic T-lymphocyte-associated antigen 4

PD-1 – programmed cell death protein 1

PD-L1 – programmed cell death protein ligand 1

Introduction to Immunotherapy Toxicities

- Requires rapid and appropriate recognition and treatment
- Clinicians are inexperienced in recognizing and treating side effects
- Patients may not be aware the adverse effect they are experiencing could be caused by ICPI treatment

Did you know?

Immunotherapy-related adverse effects can occur at any time and affect any organ

Clinical Practice Guidelines

“The Management of Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline”

“National Comprehensive Cancer Network (NCCN) Guidelines® for Management of Immunotherapy-Related Toxicities”

- Collaborative guidelines created with the goal of minimizing treatment toxicity and optimizing outcomes
- Guidelines pertain only to immune checkpoint inhibitors

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Clinical Practice Guidelines

General Principles of Management of IRAEs*

Grade	Action	Management
1 (Mild)	Continue immunotherapy	Close monitoring
2 (Moderate)	Hold immunotherapy, consider resuming when grade 1 or less	Corticosteroids may be administered
3 (Severe)	Hold with potential re-challenge, caution is advised	High dose corticosteroids
4 (Life-threatening)	Permanent discontinuation	High dose corticosteroids

*IRAEs = Immune-related adverse effects

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Meet the Patient

- BG is a 50 year-old male with no significant PMH with the exception of PD-L1 positive metastatic gastric cancer
 - He is being treated with pembrolizumab IV every 21 days
- BG presents to his oncology clinic prior to cycle 4 complaining of fatigue, nausea, and abdominal pain
- Assessment: Physical exam reveals slight yellowing of the sclera
- Laboratory values reveal the following:

Component	Result	Reference Range
ALT	262	8 - 66 unit/L
AST	178	13 - 44 units/L
Bilirubin (total)	1.1 mg/dL	0.2 - 1.2 mg/dL

Hepatotoxicity

- Incidence: 2-10 %
 - Increased to 25-30% with combination therapy
 - 15% grade 3 or higher with combination therapy
- Mechanism:
 - Lymphocytic infiltration of the hepatocytes
- Onset: 6-12 weeks
- Signs and Symptoms
 - Abdominal pain
 - Jaundice
 - Severe nausea or vomiting
 - Dark urine
 - Bleeding/bruising
 - Pruritis
 - Loss of appetite
 - Drowsiness

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Hepatotoxicity

- Diagnosis
 - Hepatic function panel
 - Rule out viral etiology
 - Rule out disease-related hepatic dysfunction
 - Rule out other drug-induced causes of transaminitis
- Adverse Events
 - Transaminitis *without* elevated bilirubin
 - Transaminitis *with* elevated bilirubin
 - Fulminant liver failure

LFTs – liver function tests

ALT – alanine aminotransferase

AST – aspartate aminotransferase

ULN – upper limit of normal

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

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Clinical Practice Guidelines – Hepatic IRAEs

Grade	Management
1 (Mild) – ALT/AST <3 x ULN	<ul style="list-style-type: none"> • CONTINUE immunotherapy • Assess LFTs with increased frequency
2 (Moderate) – ALT/AST 3-5 x ULN	<ul style="list-style-type: none"> • HOLD immunotherapy • Monitor LFTs every 3-5 days • Consider prednisone 0.5-1 mg/kg/day
3 (Severe) – ALT/AST 5-20 x ULN	<ul style="list-style-type: none"> • PERMANENTLY DISCONTINUE immunotherapy • Initiate prednisone 1-2 mg/kg/day • Consider hospital admission/hepatology consultation • Monitor liver enzymes every 1-2 days • If steroid refractory or no improvement after 3 days, consider mycophenolate 0.5-1 g every 12 hours • Infliximab should not be used for hepatitis
4 (Life-threatening) - ALT/AST >20 x ULN <p style="text-align: center;">Grade >1 transaminitis PLUS bilirubin >1.5 x ULN</p>	

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

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Hepatotoxicity

- Management
 - Consider consultation with disease-specific subspecialty
 - Limit/discontinue hepatotoxic medications
 - Early intervention with corticosteroids is the key goal of management of immune-related toxicities
 - Re-challenge can occur following a grade 1-2 IRAE when ALT/AST return to baseline and steroids have been tapered to <10 mg/day

Did you know?

Infliximab use should be avoided in patients with immune-related hepatitis, due to the risk for hepatitis B virus reactivation

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Back to the Patient

- Diagnosis:
 - **Grade 2 ICPI induced hepatotoxicity**
- Plan:
 - HOLD ICPI
 - Initiate prednisone 0.5 mg/kg/day
- Follow Up:
 - Monitor LFTs every 3 to 5 days until normalized
 - Taper prednisone as tolerated over 4 to 6 weeks
 - Consider re-challenge if appropriate and taking <10 mg prednisone daily

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Answer

According to the NCCN/ASCO clinical practice guidelines, which of the following best describes the initial recommended management of Grade 2 ICPI induced hepatotoxicity?

- A. Continue immunotherapy and monitor liver function tests
- B. Hold immunotherapy and consider corticosteroids
- C. Hold immunotherapy and administer infliximab
- D. Permanently discontinue immunotherapy

Clinical Practice Pearls

- Review patients for potential risk factors for ICPI hepatotoxicity – metastases to the liver, history of viral hepatitis, other pre-existing liver disorders
- Patients with mild hepatotoxicity can potentially be a candidate for ICPI re-challenge
- Counsel patients on signs and symptoms of severe hepatotoxicity: jaundice, itching, tea colored urine, severe abdominal pain

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

ICPI Toxicity: Cardiotoxicity

Meet the Patient

- SS is a 56 year-old female with no cardiac PMH and diagnosed with metastatic renal cell carcinoma
 - She is being treated with a combination of intravenous nivolumab and ipilimumab every 21 days and has just completed 4 cycles
- SS presents to the emergency room complaining of new onset shortness of breath, a “racing heart,” and bilateral lower extremity swelling
- Assessment:
 - Electrocardiography: T wave changes in the lateral leads, chest X-Ray: cardiomegaly, echocardiogram (ECG): impaired ventricular function
- Laboratory values reveal the following abnormalities:

Component	Result	Reference Range
Brain natriuretic peptide (BNP)	1921 pg/mL	<124 pg/mL
Erythrocyte sedimentation rate (ESR)	235 mm/hr	0-30 mm/hr

Cardiotoxicity

- Incidence: <0.1%
- Mechanism:
 - Lymphatic infiltration of the myocardium and myocardial conduction system
- Onset:
 - 2-32 weeks
 - Median onset of 10 weeks
- Signs and Symptoms
 - Shortness of breath
 - Dizziness
 - Chest pain
 - Shoulder pain
 - Arrhythmias
 - Edema

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Johnson DB, et al. *NEJM*. 2016; 375: 1749-1755.

Cardiotoxicity

- Diagnosis
 - Cardiology consultation
 - Electrocardiograph (ECG)
 - Telemetry
 - Cardiac biomarkers
 - Inflammatory biomarkers
 - Chest X-Ray, Cardiac MRI
 - Rule out other causes (viral, etc)
- Adverse Events
 - Myocarditis
 - Pericarditis
 - Arrhythmias
 - Impaired ventricular function
 - Myocardial infarction
 - Cardiogenic shock

Clinical Practice Guidelines – Cardiovascular IRAEs

Grade	Management
1 (Mild) – Asymptomatic biomarker elevation, including abnormal ECG	<ul style="list-style-type: none">• HOLD immunotherapy• Cardiology consultation
2 (Moderate) – Symptomatic biomarker elevation, including abnormal ECG	<ul style="list-style-type: none">• PERMANENTLY DISCONTINUE immunotherapy• Initiate methylprednisolone/prednisone 1-2 mg/kg/day• Hospital admission/Cardiology consultation

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National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Clinical Practice Guidelines – Cardiovascular IRAEs

Grade	Management
3 (Severe) – Arrhythmia, significant echo findings without hypotension, elevated cardiac biomarkers	<ul style="list-style-type: none">• PERMANENTLY DISCONTINUE immunotherapy• Initiate methylprednisolone/prednisone 1-2 mg/kg/day• Hospital admission/Cardiology consultation• Treat until cardiac function returns to baseline• Taper steroids over 4-6 weeks
4 (Life-threatening) – Arrhythmia, hemodynamic instability (hypotension), cardiomyopathy, cardiac biomarkers elevated >3 x ULN	<ul style="list-style-type: none">• PERMANENTLY DISCONTINUE immunotherapy• Consider methylprednisolone 1 g pulse dose• Initiate methylprednisolone/prednisone 1-2 mg/kg/day• Hospital admission/Cardiology consultation• Treat until cardiac function returns to baseline• Consider mycophenolate, infliximab, or anti-thymocyte globulin

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Cardiotoxicity

- Management
 - Holding ICPI is recommended for ALL grades of complications
 - Myocarditis symptoms are often non-specific and a diagnosis of exclusion
 - Patients with elevated troponin or conduction abnormalities should be immediately transferred to a coronary care unit
 - The appropriateness of ICPI re-challenge after cardiotoxicity is unknown

Did you know?

Infliximab use has been associated with heart failure and is contraindicated at high doses in patients with moderate to severe heart failure

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Heinzerling L, et al. *Journal for ImmunoTherapy of Cancer*. 2016; 4(50): 1-11.

Back to the Patient

- Diagnosis:
 - **Grade 3 ICPI induced cardiotoxicity**
- Plan:
 - Rapid initiation of corticosteroids
 - Inpatient admission to cardiology care unit
 - PERMANENTLY DISCONTINUE treatment due to severity IRAE
- Follow Up:
 - Cardiology consult
 - Management of heart failure symptoms per ACC/AHA guidelines

Brahmer JE et al. *J Clin Oncol*. 2018; 36: 1714-1768.

National Comprehensive Cancer Network. Guidelines for Management of Immunotherapy-Related Toxicities (Version 1.2018).

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 10, 2018.

Answer

According to the NCCN/ASCO clinical practice guidelines, which of the following best describes the recommended management of Grade 3 ICPI induced cardiotoxicity?

- A. Hold ICPI; consider resuming upon resolution of symptoms
- B. Continue ICPI and monitor cardiac biomarkers
- C. Discharge home with a prescription for prednisone
- D. Inpatient admission, cardiac work-up, cardiology consult, initiate methylprednisolone/prednisone 1-2 mg/kg/day and permanent discontinuation of ICPI

Clinical Practice Pearls

- Although rare, cardiotoxicity associated with ICPI can be rapidly progressive and potentially fatal, and is more common with combination therapy
- Manage cardiac symptoms according to the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines
- Current clinical practice guidelines recommend discontinuing ICPI if severe or life threatening cardiotoxicity occurs

Did you know?

The American College of Cardiology (ACC) curates a “Cardio-Oncology” resource page available at:

<https://www.acc.org/clinical-topics/cardio-oncology>

ICPI Toxicity: Endocrinopathy

Endocrine IRAEs

- One of the most frequently affected system
 - Pituitary, thyroid, adrenal glands, and pancreas
- Diagnosis can be challenging
 - Toxicity could be related to disease state
- Endocrine specialists play a vital role
- Essential to manage endocrine IRAEs quickly to provide optimal care and maximize benefit

Did you know?

Compared with other IRAEs, endocrine issues can have rapid improvement with treatment

Endocrine IRAEs

Anti-CTLA4 Therapy

- Primarily associated with hypophysitis and thyroid dysfunction
- Median onset 7-20 weeks
- Mechanism?
 - CTLA4 mutations leads to impaired function of CTLA4
 - Leads to unchecked T-cell self-reactivity
 - Presence of CTLA4 in normal pituitary cells could explain hypophysitis

Anti-PD1/PDL1 Therapy

- Primarily associated with thyroid dysfunction
- Median onset 10-11 weeks
- Mechanism?
 - Disruption of immune tolerance via PD1/PDL1
 - Evidence of both cellular and humoral autoimmunity have been observed in case series of insulin-dependent diabetes

Incidence

Agent	Any endocrine (%)	Any thyroid (%)	Hypo-thyroidism (%)	Hyper-thyroidism (%)	Thyroiditis (%)	Hypophysitis (%)	Primary Adrenal Insufficiency (%)
Ipilimumab	0-29	0-7.4	0-9	0-2.8	0	0-17.4	0-1.6
Pembrolizumab	0-19.2	0-19.2	0-11.5	0-7.7	0-5	0-1.2	0-4.3
Nivolumab	0-40	0-40	0-40	0-6.5	0-2.2	0-0.9	0-3.3
Avelumab	0-10	4.2-10	0-6.5	0-10	0	0	0
Atezolizumab	0-6	0-6	0-6	0	0	0-1	0
Durvalumab	2.3-11	2.3-8.7	2.3-4.8	0-3.9	0-1.2	0	0-0.4
Ipilimumab + nivolumab	16.7-50	10-50	4-27	0-30	0-4	0-11.7	0-8

Signs and Symptoms

Persistent and/or unusual headaches

Dizziness

Nausea or vomiting

Constipation

Abdominal pain

Increased sweating

Deeper voice

Muscle aches

Feeling cold

Changes in mood and/or behavior

Rapid heartbeat

Weight gain or loss

Increased urinary frequency

Increased hungry and/or thirst

Vision changes

Hair loss

Extreme fatigue

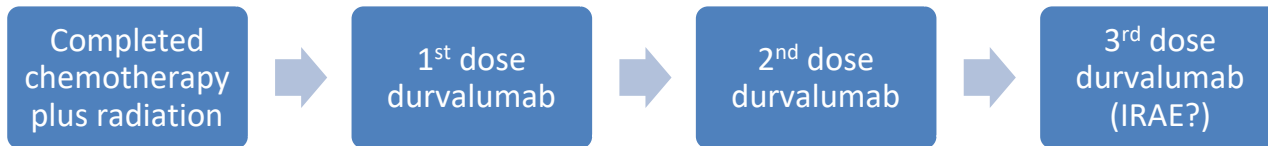
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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 2, 2018.

Meet the Patient

- MN is a 68 year-old male with a history of unresectable stage III non-small cell lung cancer
 - Completed chemotherapy plus radiation
 - Started durvalumab 10 mg/kg IV every 2 weeks
- Prior to his 3rd dose of durvalumab, he called into clinic complaining of significantly worsening fatigue and inability to walk a block without becoming winded...



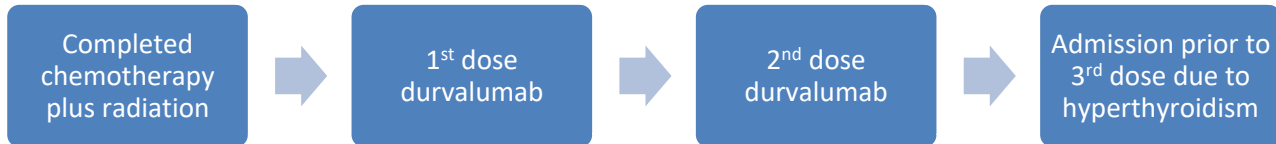
ARS Question

Which endocrine based laboratory tests need to be monitored for thyroid dysfunction with immune checkpoint inhibitors based on NCCN/ASCO clinical practice guidelines?

- A. Thyroid stimulating hormone (TSH) every 3 weeks
- B. Free thyroxine (FT4) every 3 weeks
- C. TSH and FT4 only in symptomatic patients
- D. TSH and FT4 every 4 to 6 weeks

Patient Case

- MN presents to clinic appearing anxious and diaphoretic
- Assessment:
 - Rapid irregular heartbeat
 - FT4 = 15 ug/dL
 - TSH = 0.01 mIU/L
 - ACTH and cortisol are normal
- Diagnosis:
 - Grade 2 ICPI induced hyperthyroidism
- Plan:
 - Direct admission, cardiology consult, IV beta-blockers



Hyperthyroidism Management

Grade	Description	Management
1	Asymptomatic or mild symptoms	Continue ICPI Monitor TSH, FT4 every 2-3 weeks (eval for persistent hyperthyroidism)
2	Moderate symptoms, able to perform ADL	Consider holding ICPI Consider Endocrine consult Beta-blockers, hydration, supportive care > 6 weeks (persistent hyperthyroidism): work-up
3-4	Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPI Beta blocker, hydration, supportive care Severe symptoms or concern for thyroid storm: hospitalize and initiate prednisone 1-2 mg/kg/d or equivalent tapered over 1-2 weeks

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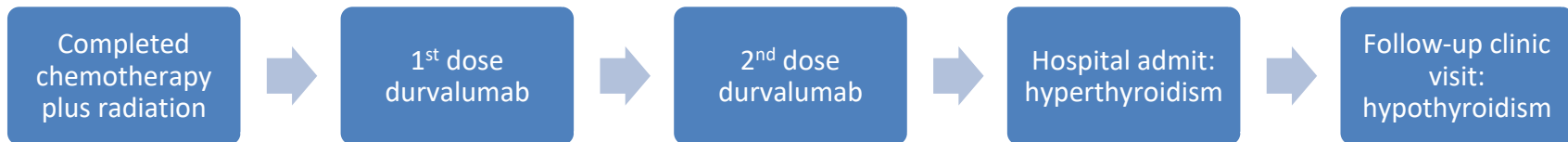
ARS Question

After diagnosis of ICPI related hyperthyroidism, what laboratory monitoring needs to occur?

- A. TSH and FT4 every 4 weeks
- B. TSH and FT4 every 2 to 3 weeks
- C. TSH every 4 to 6 weeks
- D. FT4 every 4 to 6 weeks

Patient Case

- Two weeks after discharge, MN returns to clinic
- Assessment:
 - Worsening fatigue, constipation, and depression
 - TSH = 12 mIU/L
 - T4 = 0.2 mcg/dL
 - Obtain endocrine consult
- Diagnosis:
 - Grade 2 ICPI induced hypothyroidism
- Plan:
 - Taper beta-blocker
 - Start levothyroxine



Hypothyroidism Management

Grade 1

- Continue ICPI
- Monitor TSH and FT4

TSH < 10 mIU/L and asymptomatic

Grade 2

- Consider holding ICPI and endocrine consult
- Thyroid supplementation (any degree of TSH elevation or asymptomatic with TSH levels that persist > 10 mIU/L)
 - No risk factors: 1.6 mcg/kg/d (IBW); if elderly or frail with multiple comorbidities: consider titrating up from low dose (25-50 mcg)
- Monitor TSH Q6-8 weeks while titrating hormone replacement to normal TSH, afterwards monitor thyroid function Q6 weeks

Moderate symptoms;
able to perform ADL;
TSH persistently > 10 mIU/L

Grade 3 & 4

- Hold ICPI and obtain endocrine consult
- May admit for IV therapy if signs of myxedema
- Thyroid supplementation

Severe symptoms,
medically significant or life-threatening consequences,
unable to perform ADL

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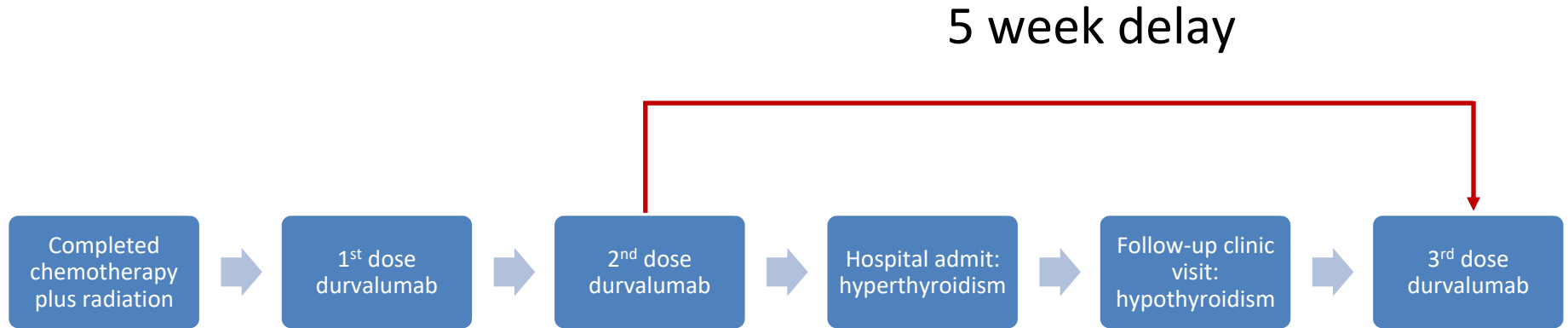
ARS Question

What dose of levothyroxine should MN be started on?

- A. 75 mcg PO daily
- B. 100 mcg PO daily
- C. 150 mcg PO daily
- D. 200 mcg PO daily

PMH: HTN, anxiety
Weight = 70 kg
All other labs WNL

Patient Case



Clinical Practice Pearls

- Endocrinopathies often result in permanent organ damage that require life-long hormonal supplementation
- Endocrinopathies can have rapid improvement with treatment
- Corticosteroids help mitigate acute inflammation but are not recommended for managing hypothyroidism or type I diabetes

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ICPI Toxicity: Dermatologic

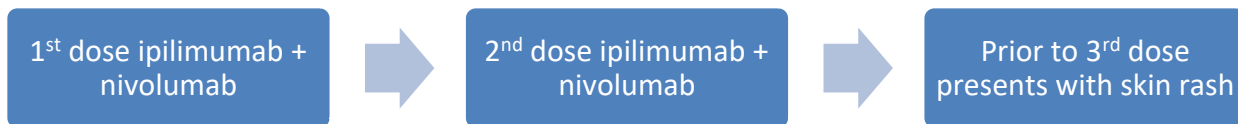
Meet the Patient

- MJ is a 66 year-old female with newly diagnosed metastatic melanoma who presents to clinic for initiation of ipilimumab and nivolumab
 - PMH: left cataract removal, degenerative joint disease
 - PSH: left knee arthroscopy, and s/p sinus surgery for deviated septum
 - Allergies: sulfa (skin rash), intolerant of aspirin
 - ECOG performance status: 0
 - Medications: loratadine, omega-3 fish oil, sertraline, vitamin D
- As the clinic pharmacist, you enroll the patient in the immune checkpoint inhibitor program

Initiation of
ipilimumab +
nivolumab

Patient Case

- MJ presents prior to cycle 3 of ipilimumab and nivolumab
 - During RPh follow-up phone call, she reported a mild rash on her upper chest
 - Managed with topical hydrocortisone 2.5% cream and occasional use of oral diphenhydramine
 - Today, she reports that rash has been increasing in size and remains pruritic
- Assessment:
 - A few scattered areas of rash on the upper chest, abdomen, arms, and upper thighs
 - Estimation rash involved 15-20% of BSA



Dermatologic IRAEs

- Cutaneous toxicities appear to be one of the most prevalent IRAEs
 - Anti-CTLA-4, anti-PD-1, anti-PD-L1 all implicated
 - Anti-CTLA-4 and anti-PD-1 therapies in combination are associated with more frequent, severe and earlier cutaneous IRAEs
- Observed in more than 1/3 of treated patients
 - Regardless of tumor type
- Onset is within the first several weeks of treatment
- Most common is maculopapular rash (eczema-like spongiotic dermatitis) and pruritus
- Early recognition and management can mitigate severity of lesions

Dermatologic IRAEs

Anti-CTLA4, -PD1, -PDL1 Therapy

Maculopapular rash	Vitiligo	Psoriasis
Lichenoid reactions	Life threatening (Stevens-Johnson syndrome, toxic-epidermal necrolysis)	Grover's Disease
Pruritus	Bullous Pemphigoid	Dermatomyositis
Vasculitis	Sjogren's Syndrome	Sarcoidosis
Sweet's syndrome	Acneiform rash	Papulopustular Rosacea
Alopecia	Nail changes	Photosensitivity

Dermatologic IRAEs

Grade	Description	
1	Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Papules and/or pustules covering <10% BSA, +/- pruritus or tenderness
2	Inflammatory reaction that affects quality of life and requires intervention based on diagnosis Limiting instrumental ADL	Papules and/or pustules covering 10-30% BSA, +/- pruritus or tenderness
3	As grade 2, but with failure to respond to indicated interventions for a grade 2 dermatitis Limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering >30% BSA, +/- pruritus or tenderness
4	All severe rashes unmanageable with prior interventions and intolerable Associated with extensive superinfection with IV antibiotics indicated; life threatening consequences	Papules and/or pustules covering any percent BSA, ±pruritus or tenderness

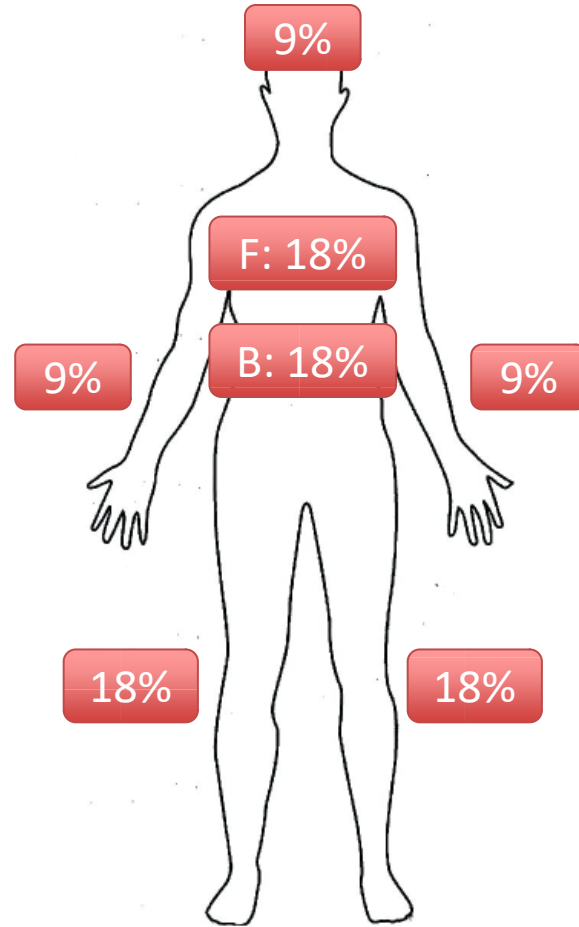
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Common Terminology Criteria for Adverse Events (CTCAE) 2017 v.5.0

Rash BSA Calculation



ARS Question

What grade of dermatologic toxicity is MJ experiencing?

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

Dermatologic IRAE Management

Grade 1	<ul style="list-style-type: none">• Topical emollients and/or mild-moderate potency topical corticosteroids• Avoid skin irritants and sun exposure	Continue ICPI
Grade 2	<ul style="list-style-type: none">• Consider initiating prednisone (or equivalent) at 1 mg/kg, tapering over at least 4 weeks• Treat with topical emollients, oral antihistamines, and medium to high potency topical corticosteroids	Consider holding ICPI, monitor weekly for improvement
Grade 3	<ul style="list-style-type: none">• Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks• Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids	Hold ICPI, consult dermatology for resumption
Grade 4	<ul style="list-style-type: none">• Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, with slow tapering	Hold ICPI indefinitely unless benefits outweigh risks

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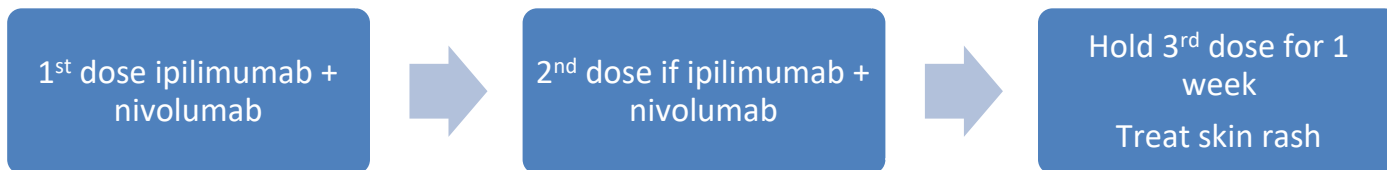
Potency of Common Topical Corticosteroids

Potency	Medication Name	Strength	Dosage vehicle
Least potent	Hydrocortisone	0.5-2.5%	C, L, O
Low	Desonide	0.05%	G, L, O
	Fluocinolone acetonide	0.01%	C
Medium	Betamethasone valerate	0.1%	C, L
	Fluocinolone acetonide	0.025%	C, O
	Mometasone furoate	0.1%	C, L, O
	Triamcinolone	0.025-0.1%	C, L, O
Medium to High	Betamethasone dipropionate	0.05%	C
	Fluticasone propionate	0.005%	O
	Triamcinolone	0.5%	C, O
High	Augmented betamethasone dipropionate	0.05%	C, L
	Betamethasone dipropionate	0.05%	O
	Fluocinonide	0.05%	C, G, O
Ultra-high	Augmented betamethasone dipropionate	0.05%	G, O
	Clobetasol	0.05%	C, G, L, O
	Fluocinonide	0.1%	C

C=cream, G=gel, L=lotion, O=ointment

Patient Case

- Diagnosis:
 - Grade 2 ICPI induced skin rash
- Plan:
 - Hold ipilimumab/nivolumab x 1 week
 - Patient would like to avoid oral steroids
 - Start other supportive care medications
 - Follow-up in 1 week



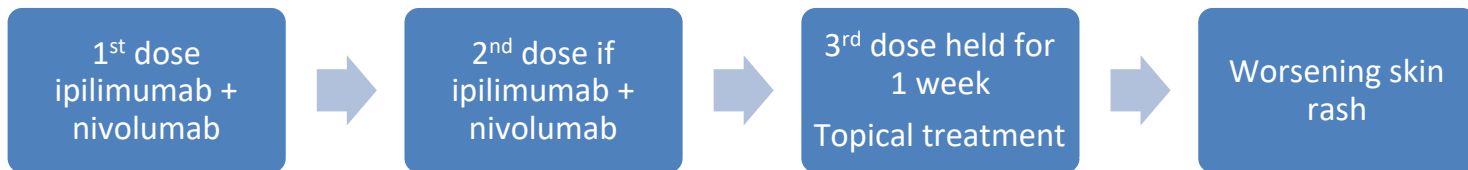
ARS Question

Based on MJ's grade of toxicity, which therapy would you recommend?

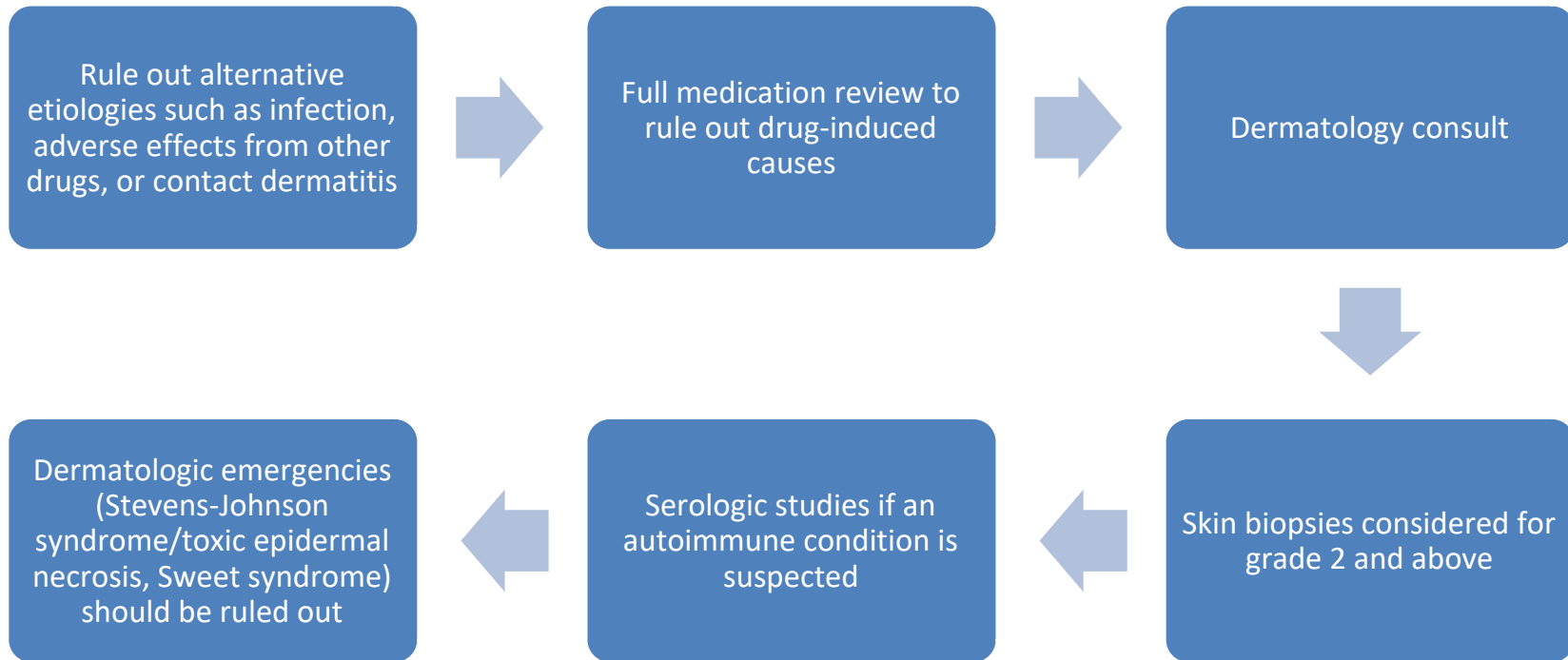
- A. Clobetasol 0.05% cream applied twice daily and hydroxyzine 25 mg PO TID PRN
- B. Diphenhydramine topical cream applied twice daily and diphenhydramine 25 mg PO BID PRN
- C. Hydrocortisone 2.5% cream applied twice daily and diphenhydramine 25 mg PO BID PRN
- D. Triamcinolone 0.5% cream applied twice daily and hydroxyzine 25 mg PO TID PRN

Patient Case

- MJ presents back to clinic 1 week later
 - Rash continued to worsen
 - Woke up with new facial edema and erythema
- Assessment:
 - Disseminated, maculopapular and erythematous rash covering approximately 50% of BSA on back, chest, arms, and legs
- Diagnosis:
 - Grade 3 ICPI induced skin rash



Diagnostic Work-Up



ARS Question

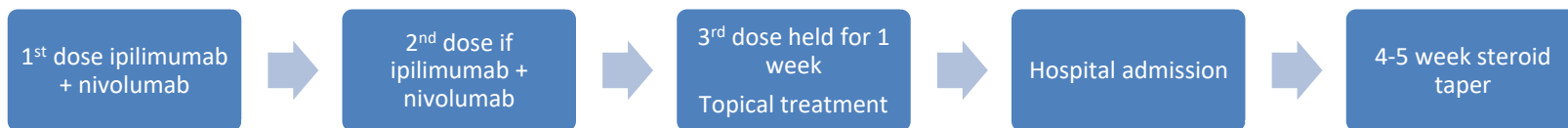
Based on MJ's grade 3 skin IRAE, what would the best treatment option be?

- A. Continue ICPI, admit for IV methylprednisolone 1 mg/kg/day
- B. Continue ICPI, admit for PO prednisone 2 mg/kg/day
- C. Hold ICPI, admit for IV methylprednisolone 1 mg/kg/day
- D. Hold ICPI, admit for PO prednisone 0.5 mg/kg/day

Patient Case

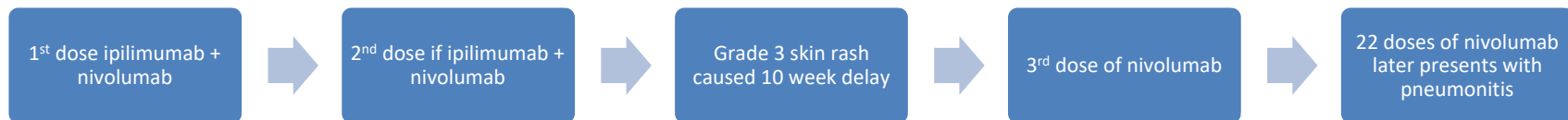
- MJ presents to clinic 1 week after discharging from the hospital
- Plan:
 - Taper prednisone over at least 4 weeks
 - Consult dermatology when and if appropriate to resume ICPI
 - Continue topical emollients, oral antihistamines, and topical steroids

Week	Prednisone Dose
1	60 mg PO daily
2	40 mg PO daily
3	20 mg PO daily
4	10 mg PO daily
5	5 mg PO daily



Patient Case

- MJ presents back to clinic, her skin rash is completely resolved
 - Ipilimumab will be discontinued due to grade 3 rash
 - She will resume single agent nivolumab every 2 weeks
- Fast forward 11 months...
 - CT and MRI findings show stable disease
 - MJ reports an occasional nonproductive cough which started 3 weeks ago
 - Increasing dyspnea on exertion
 - She denies fever, headache, chills, nausea/vomiting, rash, abdominal pain
 - CT chest shows new consolidations concerning for immune-mediated pneumonitis



Pneumonitis Management

Grade	Description	
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Confined to one lobe of the lung or < 25% of lung parenchyma
2	Symptomatic; medical intervention indicated; limiting instrumental ADL	Involves more than one lobe of the lung or 25-50% of lung parenchyma
3	Severe symptoms; limiting self-care ADL, oxygen indication	Involves all lung lobes or > 50% of lung parenchyma
4	Life-threatening; urgent intervention indicated (intubation)	

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https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed August 2, 2018.

Pneumonitis Management

Grade 1	<ul style="list-style-type: none">• Monitor patients weekly, repeat CT in 3-4 weeks	Permanently discontinue ICPI
Grade 2	<ul style="list-style-type: none">• Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks• If no improvement after 48-72 hours, treat as Grade 3/4• Consider empirical antibiotics	Hold ICPI until resolution to Grade 1 or less
Grade 3 & 4	<ul style="list-style-type: none">• Initiate (methyl)prednisolone IV 1-2 mg/kg/d, taper over 4-6 weeks• No improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice daily or IVIG for 5 days or cyclophosphamide	Hold ICPI, resume once radiographic improvement or resolution

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Clinical Practice Pearls

- Patients should be educated to be hypervigilant of their skin and should report any changes
- Recognize differences in topical steroid preparations and strengths
- Patients can have multiple IRAEs over the course of ICPI treatment

Did you know?

Pruritus can occur with or without rash. Treatment of severe pruritus requires corticosteroids and GABA antagonist

Pharmacist's Role in Management

- Recognize appropriate corticosteroid tapers
 - Some IRAEs require over at least one month and can be escalated when needed
- Recommend appropriate supportive care medications
 - Prophylaxis against *pneumocystis jiroveci pneumonia* (PJP)
 - Prednisone dose of 20 mg or more daily for 4 or more weeks
 - Prophylaxis against fungal infections
 - Prednisone dose of 20 mg or more daily for more than 6-8 weeks
 - Proton pump inhibitors or H2 blockers can be considered in patients at higher risk of gastritis for the durations of corticosteroid therapy
- Develop and implement an ICPI toxicity monitoring program

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ICPI Toxicity KEY TAKEAWAYS

- 1) *Ensure patients receive appropriate education about ICPI and their associated toxicities*
- 2) *Early recognition and management can lead to better outcomes*
- 3) *Pharmacists play a vital role in ensuring appropriate treatment and supportive care*



**A Whole New World:
A Case-Based Approach to Managing
CAR T-Cell Therapy and Immunotherapy Toxicities**

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