Updates on Oncologic Emergencies, Including Side Effects of New Therapies

Gerald Hsu, MD, PhD
Assoc. Clinical Professor of Medicine
University of California, San Francisco

Disclosures

I have nothing to disclose

Outline

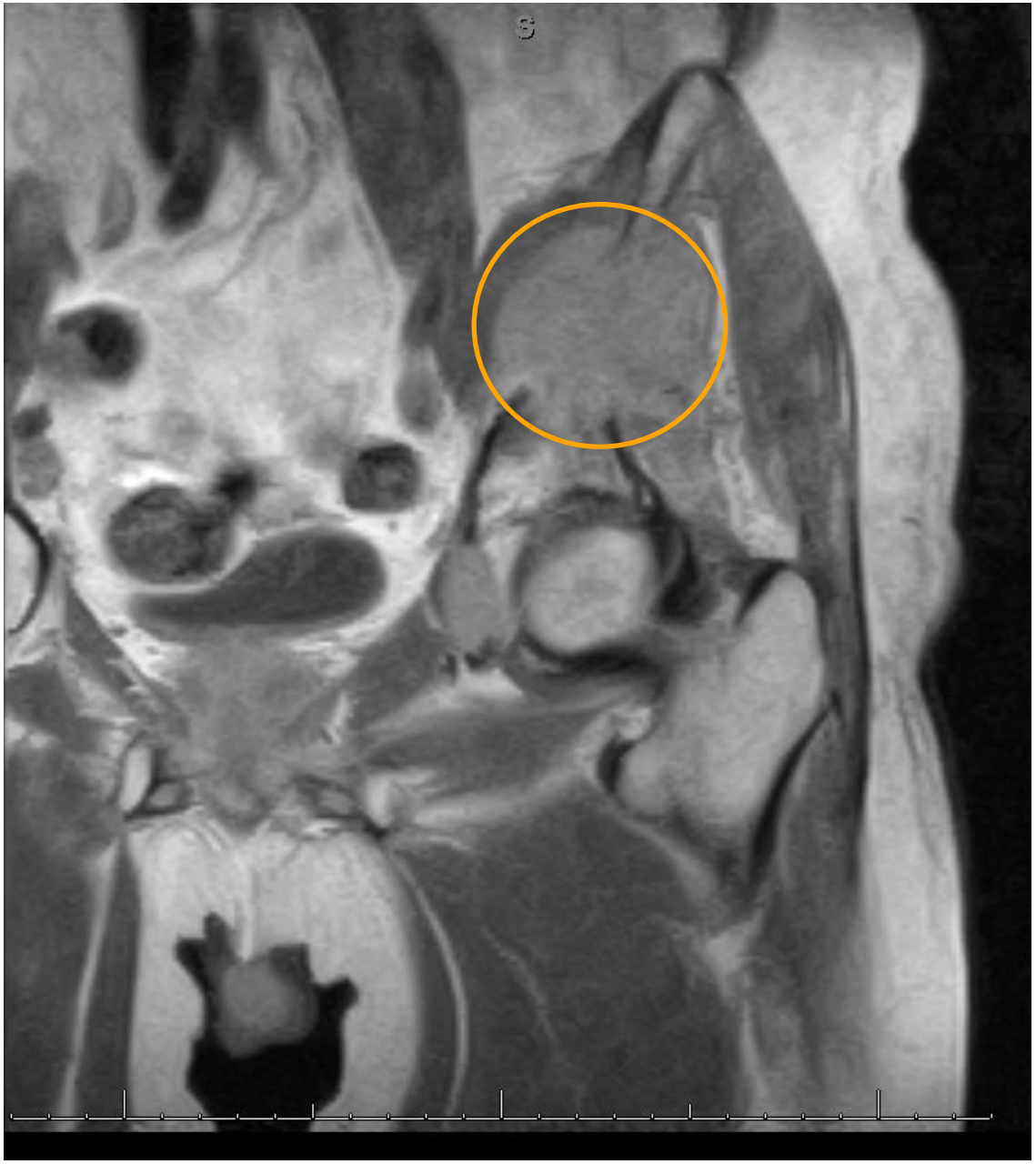
- **Updates on oncologic emergencies:**
  - **Hypercalcemia**
  - **Tumor lysis syndrome**
  - **Thrombocytopenia**

- **Review of uses and side effects of immunotherapies**

Hypercalcemia | *Old and new*

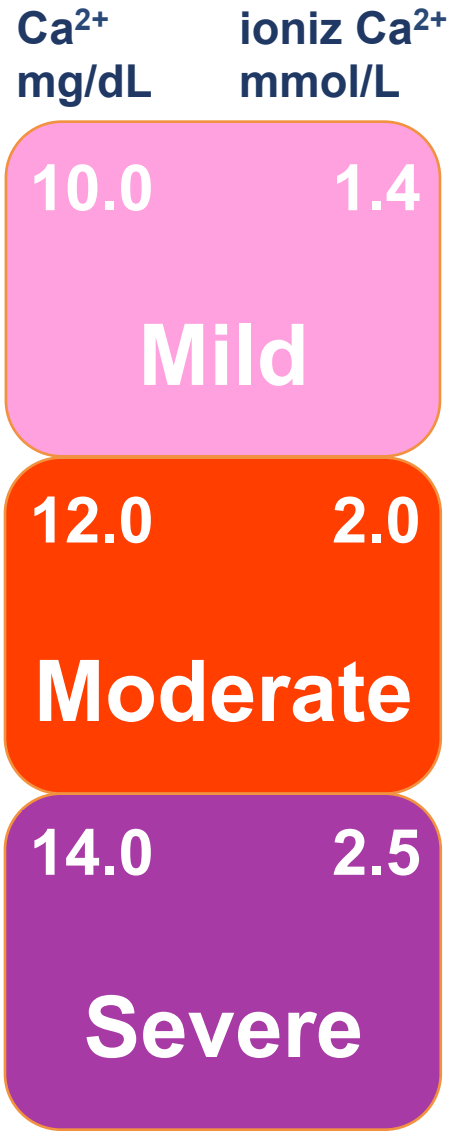
- **Mr. N: 72M with multiple myeloma.**
  - **Dx:** 5/2015 in setting of long-standing MGUS (since 2003)
  - **Prognostic info:** IgG kappa, +lytic bone lesions, FISH without high-risk mutations
  - **Treatment:**
    - 6/2015-10/2015: Velcade, cyclophosphamide, dexamethasone
      - **PR**
    - 10/2015: Lenalidomide, dexamethasone
      - **CR**

Progressive hip pain and diminished concentration.


S

Hypercalcemia | *Manifestations*

- Progressive mental impairment and renal failure.
- A poor prognostic sign.
- Treatment is indicated if hypercalcemia is symptomatic or severe.



Hypercalcemia | *Mechanisms*

type	mechanism	Associated cancers
Humoral	PTHrP	• Squamous cancers (most commonly lung) • Breast cancer • Renal cancer • Ovarian or endometrial cancer
Osteolytic	Cytokine mediated and PTHrP	• Multiple Myeloma • Breast cancer • Lymphoma

Much less common:

- **$1,25(OH)_2D$ secreting tumors (lymphomas)**
- **PTH secreting tumors**

Hypercalcemia | *Review*

volume repletion and supportive care
- NS 200-300 cc/hr
- oral phos repletion (goal 2.5-3 mg/dL)

bring down the calcium
- bisphosphonate +/- calcitonin
  - either pamidronate or zoledronate
- response time: hours for calcitonin; about a day with bisphophonate
- duration: up to 4 weeks

treat underlying cause

Hypercalcemia | *New(ish)!*

Options for treating severe hypercalcemia in AKI (Cr >4.5)

- Full dose bisphosphonate
- Reduced dose bisphosphonate with slower infusion rate
    - (eg. 4 mg zoledronic acid over 1 hour or 30 mg pamidronate over 4 hours)
- Calcitonin until kidney function improves
- RANK ligand inhibitor (ie. denosumab) that is not renally cleared.

Outline

- **Updates on oncologic emergencies:**
  - Hypercalcemia
  - **Tumor lysis syndrome**
  - Thrombocytopenia
- Review of side effects of immunotherapies

Tumor Lysis Syndrome | *Old and New*

- **Mr. T: 70M with CLL with wbc count of 150,000/uL, progressive anemia and bulky adenopathy.**
  - **Prognostic info:** FISH testing revealed presence of deletion 17p.
  - **Treatment:** Considering ibrutinib or venetoclax with or without rituximab.

Tumor Lysis Syndrome | *Review*

Definition: A syndrome resulting from “the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy.”

— Cairo & Bishop

Laboratory tumor lysis = 2 or more electrolyte abnl

- **K > 6 mEq/L**
- **Phos > 4.5 mg/dL**
- **UA > 8 mg/dL**
- **Ca < 7 mg/dL**

} ***or 25% change from baseline***

Clinical tumor lysis = laboratory tumor lysis AND

- **Cr 1.5x ULN or**
- **cardiac arrhythmia/sudden death or**
- **seizure**

Tumor Lysis Syndrome | *Review + new*

HIGH	MEDIUM	LOW
Burkitt lymphoma/ leukemia	CLL	Multiple Myeloma
High grade DLBCL	NHL with elevated LDH	CML
ALL (wbc >100K)	ALL (wbc <100K)	Other solid tumors
AML (wbc >100K)	AML (wbc <100K)	
CLL with high burden disease + venetoclax	small cell lung cancer	
	germ cell tumors	

Tumor Lysis Syndrome | *Review*

- **Fluids**
  - 2-3 L/m2/day. (D5 1/4 NS preferable)

- **Hypouricemic agents**
  - allopurinol if uric acid is wnl
    - Caution with patients of Asian descent (due to inheritance of HLA allele that predisposes to severe cutaneous rxns)
  - rasburicase if high-risk or elevated uric acid in intermediate-risk patients
    - exception is patients with G6PD deficiency
    - **In practice, 3 mg dose is commonly used**

- **Monitoring**
  - For patients at high-risk, serum K, Cr, Ca, Phos, uric acid, LDH q4-8H (in addition to 4 hours after first rasburicase dose)
  - Urine output (2 ml/kg/hr)

Outline

- **Updates on oncologic emergencies:**
  - Hypercalcemia
  - Tumor lysis syndrome
  - **Thrombocytopenia**

- Review of side effects of immunotherapies

Thrombocytopenia | *Review*

- **Mr. J: 54M with h/o hypertension, CKD, and sickle cell trait presents with 2 weeks abdominal pain, nausea, and vomiting.**

MEDS:

Atorvastatin
Amlodipine
Carvedilol
Labetalol
Pantoprazole
Senna

EXAM:

-AF 192/130 116
-Lungs with bibasilar crackles bilaterally.
-Abd soft, NT, ND.
-Neuro non-focal.
-Skin with petechiae.

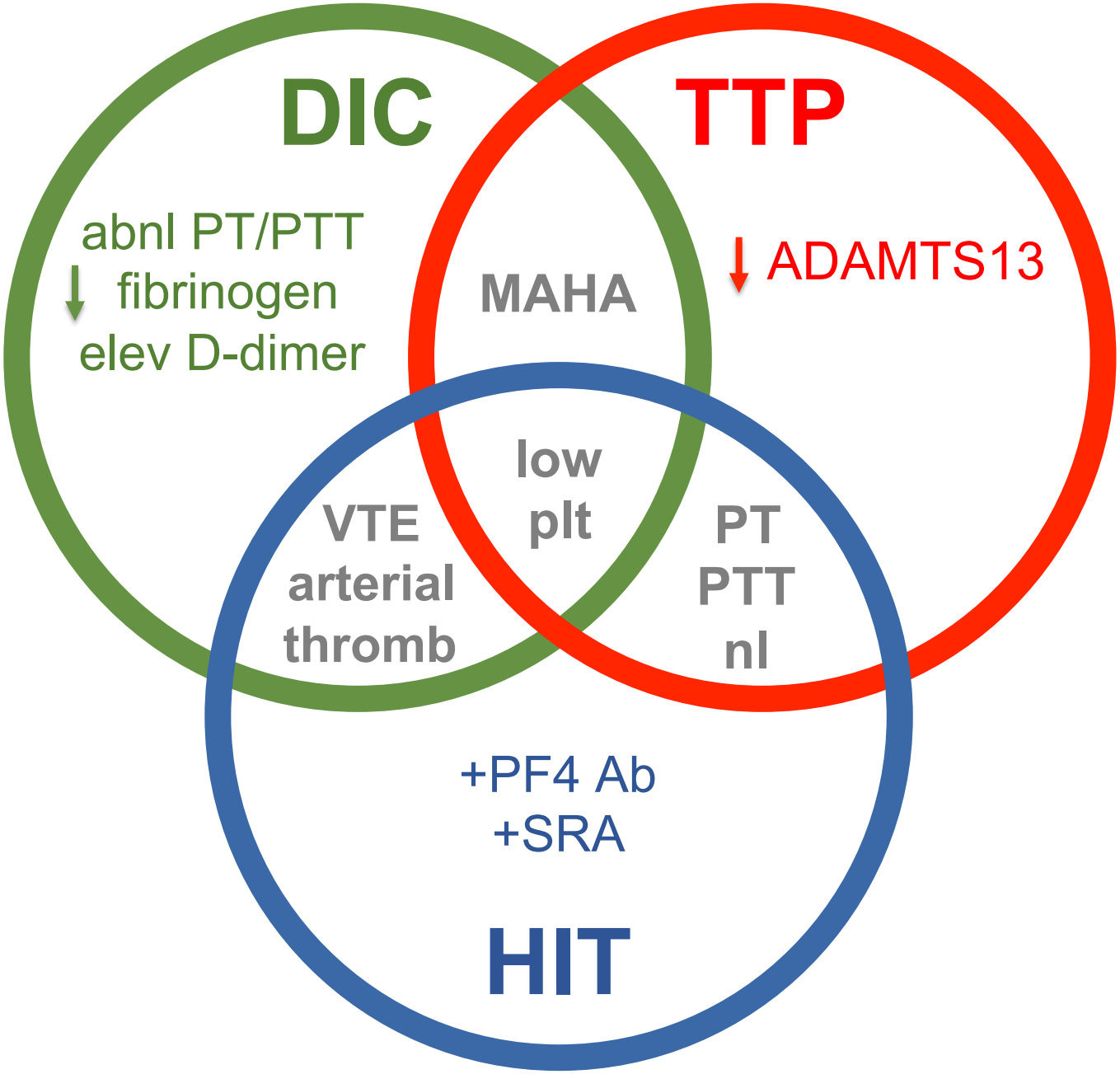
IMAGING:

-CT chest/abdomen without acute findings.
-U/S of kidneys with moderate echogenicity bilaterally.

LABS:

wbc 12.4 hb 7.9 plt 69
LDH 719 U (140-271)
T bili 1.0 mg/dL (0.1-1.2)
PT 14.2 s INR 1.1
PTT 31.4 s (wnl)

Smear: "Few schistocytes with additional RBC fragments and blister cells. May be consistent with microangiopathic hemolytic anemia."


DIC
abnl PT/PTT
fibrinogen
elev D-dimer
TTP
ADAMTS13
MAHA
low
plt
VTE
arterial
thromb
PT
PTT
nl
+PF4 Ab
+SRA
HIT

Thrombocytopenia | *Drug induced*

Most common:

- Antibiotics:
  - vancomycin
  - penicillin
  - ceftriaxone
  - TMP/SMX
  - rifampin
- Gp IIb/IIIa inhibitors
- ibuprofen
- quinine

New onset thrombocytopenia

↓

Plt <20K ?
Mucocutaneous bleeding?
Time course: 5-10 days or <1 day)?

↓ **YES!**

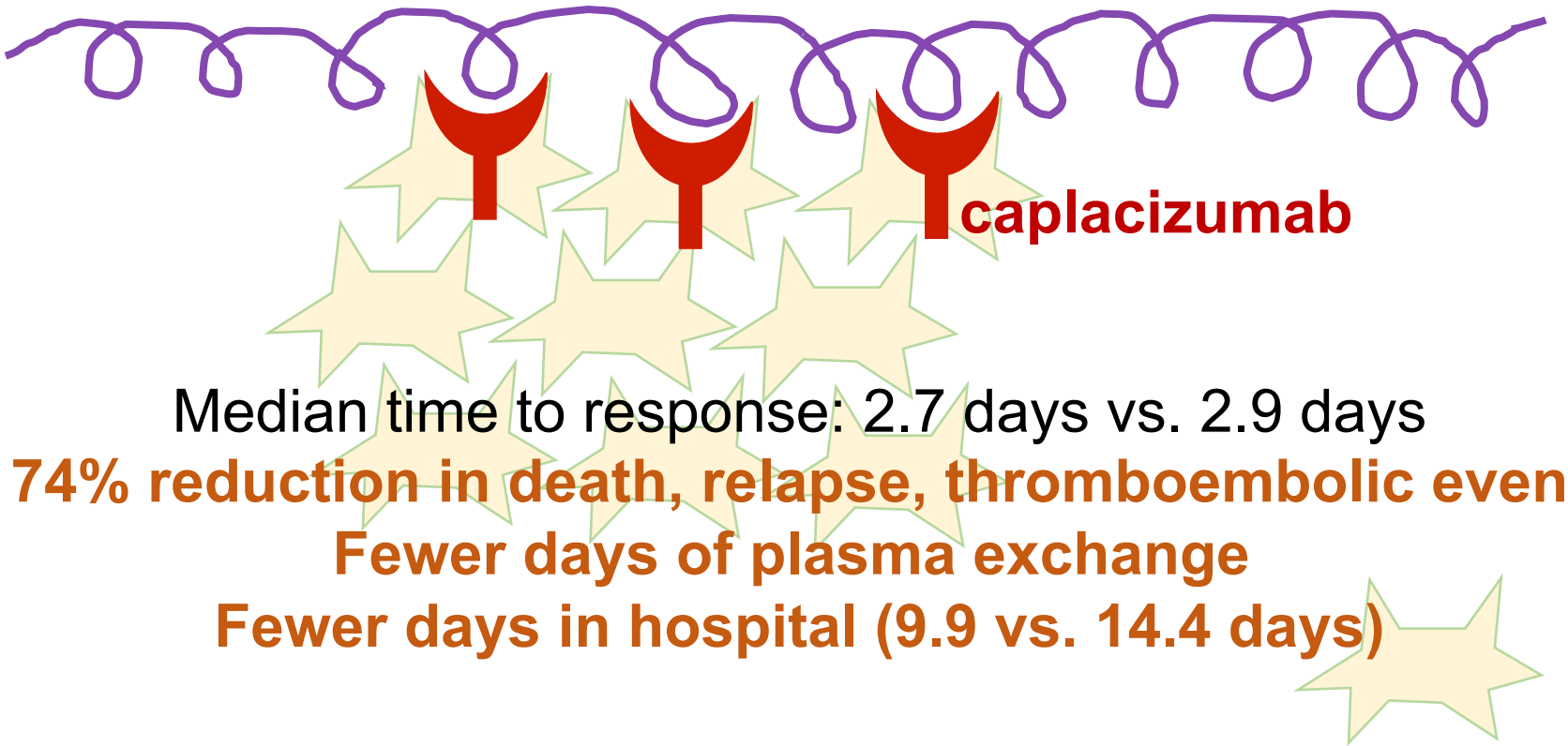
Known offender?

↓ **YES!**

Stop the drug.
Transfuse. Consider IVIG and steroids.
Call hematology or lab medicine to test for drug dependent platelet antibodies.

Adapted from Arnold, DM et al. Transfus Med Rev (2013) 27:137.

Thrombocytopenia | *NEW! For TTP…*



Median time to response: 2.7 days vs. 2.9 days

74% reduction in death, relapse, thromboembolic event

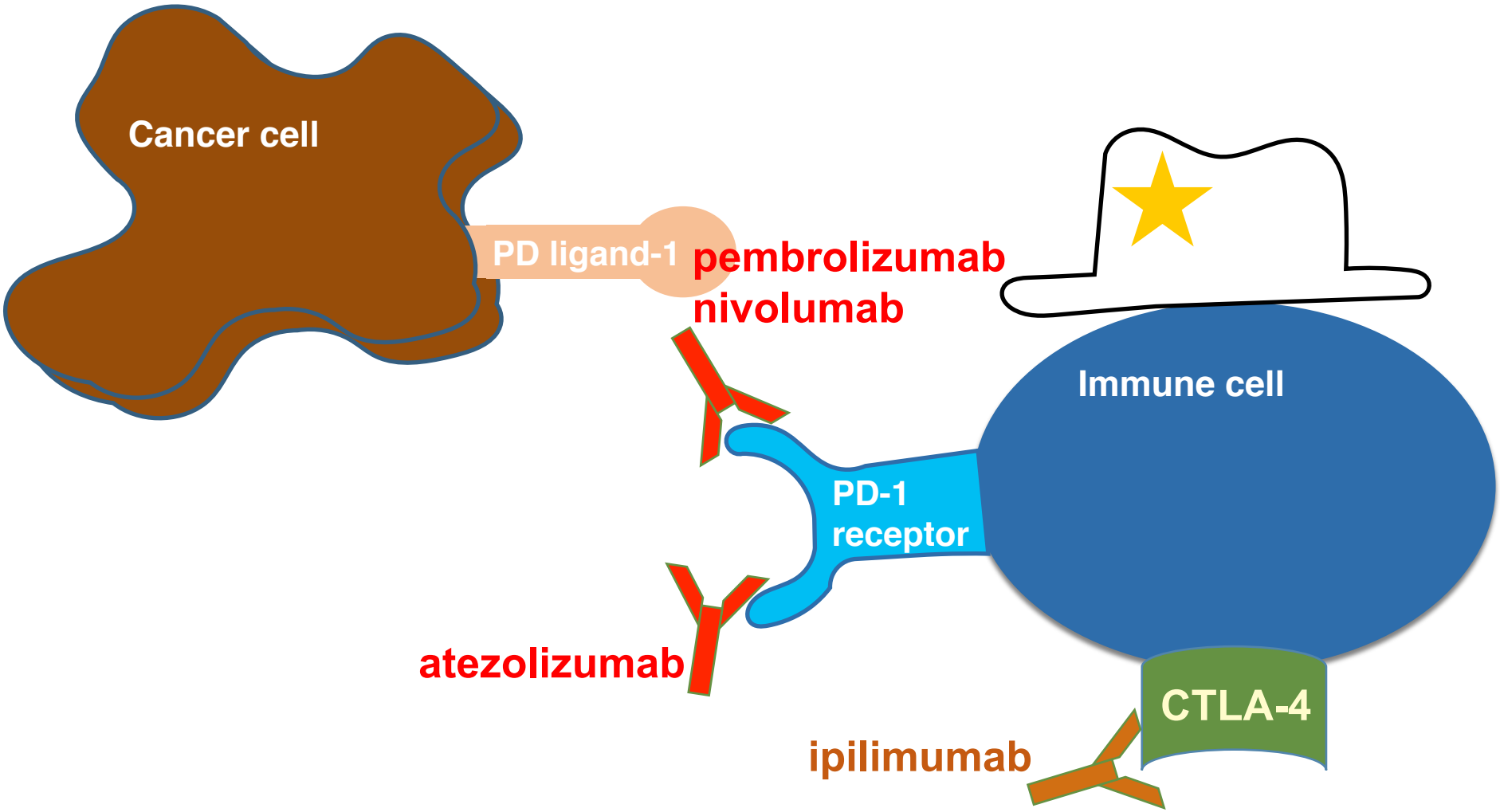
Fewer days of plasma exchange

Fewer days in hospital (9.9 vs. 14.4 days)

Outline

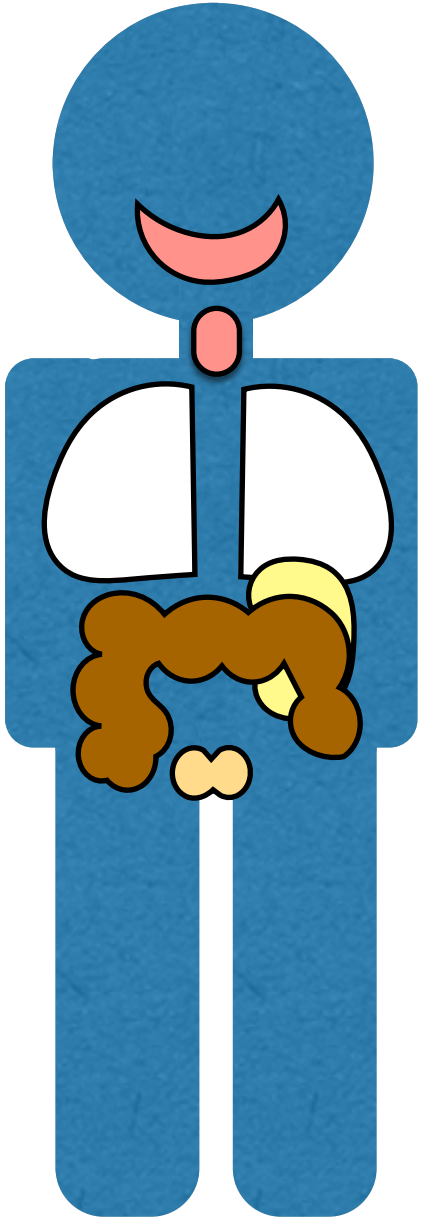
- Updates on oncologic emergencies:
  - Hypercalcemia
  - Tumor lysis syndrome
  - Thrombocytopenia

- **Review of side effects of immunotherapies**



“Leave me alone” “You don’t look like you’re from around here”

2014	Melanoma
2015	Lung
	Renal cell
2016	Head & neck
	Hodgkin lymphoma
2017	DNA repair deficiency, MSI-high
	Bladder
2018	Hepatocellular
	Cervical
2019	Breast Cancer (triple neg)



2018
TOP 5 ONC DRUGS

1. Lenalidomide
2. Nivolumab (+31%)
   $7.6 billion
3. Pembrolizumab (+88%)
   $7.2 billion
4. Trastuzumab
5. Bevacizumab

Checkpoint inhibitors | *Adverse effects*

What are the most common side effects? And what are the side effects that are unique to checkpoint inhibitors?

When do these side effects typically develop?

How do I manage immune-related adverse events?

Checkpoint inhibitors | *Adverse effects*

- **Mr. S: 71M with metastatic melanoma.**
  - **Dx:** 9/2014 in setting evaluation for anemia and weight loss revealing lung and renal masses.
  - **Staging:** Metastatic. Lung, renal, small bowel, brain, and spine lesions.
  - **Treatment:**
    - 10/2014-2/2015: Ipilimumab
      - **PR with progression of disease in brain**
    - 3/2015-presentation: Pembrolizumab

Maculopapular rash on back.

Checkpoint inhibitors | *Adverse effects*

RASH: The most common adverse event

When? Usually within the first few weeks.

Biopsy? Yes. Rule out TEN, DRESS, etc.

Management:
-Does not affect quality of life (**grade 1**): mild-mod potency topical steroids and emollients. Oral antihistamine.
-Affects quality of life (**grade 2**): Consider oral steroids and holding CPI. Higher potency topical steroid.
-Refractory to above therapy **(grade 3+)**: Hold CPI. Oral/ IV steroids.

Adverse events: General

Skin (7%)
GI (6%)
Musculoskeletal (3%)
Endocrine (2%)
Nervous system (2%)
Respiratory (1%)
Blood/lymphatic (1%)

Adverse events: Immune

Skin (10%)
  -rash
  -pruritis
  -vitiligo
GI
Musculoskeletal (2%)
Endocrine (2%)

Checkpoint inhibitors | *Adverse effects*

- **Mr. G: 58M with metastatic melanoma.**
  - **Dx:** 2/2019 in setting of SBO.
  - **Staging:** metastatic. Small bowel, lungs
  - **Treatment:**
    - 3/2019: Nivolumab.
      - **Mixed response**
    - 6/2019: Nivolumab + ipilimumab

Diarrhea.

Checkpoint inhibitors | *Adverse effects*

IMMUNE RELATED COLITIS:
Depends on drug.

- Anti-CTLA4 (ipilimumab): ~30%
- Anti-PD1 (nivolumab): ~1-2%

When? Approximately 6 weeks.

Management depends on degree:
-**Grade 1 (less than 4 stools/d):** Loperamide.
-**Grade 2 (4-6 stools/d):** Hold CPI. Labs/stool testing for infectious etiologies; consider CT scan and endoscopy. Steroids.
-**Grade 3 (7+ stools/d):** Steroids +/- infliximab. Consider endoscopy. Consider permanent CPI discontinuation.

Checkpoint inhibitors | *Adverse effects*

- **Mr. T: 70M with metastatic lung cancer.**
  - **Dx:** 4/2014 in setting of evaluation for anemia and weight loss.
  - **Staging:** IIIA (4/2014); metastatic (7/2014). Bilateral lungs, pleural with effusion.
  - **Treatment:**
    - 4/2014: Chemoradiation
    - 10/2014: Carboplatin/pemetrexed followed by pemetrexed maint.
      - **SD**
    - 8/2015: paclitaxel/trastuzumab
      - **SD**
    - 9/2016: nivolumab

Monitoring labs reveal a transaminitis (2.5 x ULN)

Checkpoint inhibitors | *Adverse effects*

IMMUNE RELATED HEPATITIS:
Relatively common ~1-10%.

When? Usually within the first few weeks (~8).

Management depends on degree:
-**Grade 1 (less than 3x ULN):** No intervention.
-**Grade 2 (3-5x ULN)**, Recheck in 3 days. Steroids if LFTs rising.
-**Grade 3 (5-20x ULN) AND normal bili/albumin:** Stop CPI. Daily LFTs. Oral prednisolone 1 mg/kg/day.
-**Worse than above:** Stop CPI. IV methylprednisolone 2 mg/kg/day; consider mycophenolate mofetil.

Adverse events: Pembro

Skin (10%)
  -rash
  -pruritis
  -vitiligo
GI
Musculoskeletal (2%)
Endocrine (2%)

Adverse events: Nivo

Skin (24%)
GI (15%)
Hepatic (12%)
Pulmonary (5%)

Checkpoint inhibitors | *Adverse effects*

- **Mr. T: 70M with metastatic lung cancer.**
  - **Dx:** 4/2014 in setting evaluation for anemia and weight loss.
  - **Staging:** IIIA (4/2014); metastatic (7/2014). Bilateral lungs, pleural with effusion.
  - **Treatment:**
    - 4/2014: Chemoradiation
    - 10/2014: Carboplatin/pemetrexed followed by pemetrexed maint.
      - **SD**
    - 8/2015: paclitaxel/trastuzumab
      - **SD**
    - 9/2016: nivolumab
      - **SD**

Mild increase in fatigue and decreased appetite.

OPDIVO (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

Patient Monitoring Checklist

OPDIVO (nivolumab) + YERVOY (ipilimumab)
REGIMEN

Patient name _____ **Date** _____

This checklist is intended for nurses or other healthcare professionals (HCPs) to use prior to dosing each patient and at any follow-up visits or calls with the patient to identify some of the signs and symptoms associated with adverse reactions related to treatment with OPDIVO® or the OPDIVO + YERVOY® Regimen. Early identification of adverse reactions and intervention are important parts of the safe use of OPDIVO and the OPDIVO + YERVOY Regimen.

OPDIVO (10 mg/mL) and YERVOY (5 mg/mL) are injections for intravenous (IV) use.

Please note: this checklist is not meant to be all inclusive.

If the patient responds "Yes" to any of these questions, consult with the patient's HCP before administering OPDIVO.

QUESTION	RESPONSE		NOTES
GENERAL			
Are you having difficulty performing your normal activities?	Yes ☐	No ☐	
Have you had constant or unusual headaches?	Yes ☐	No ☐	
Have you felt drowsy or extremely tired?	Yes ☐	No ☐	
Have you felt dizzy or fainted?	Yes ☐	No ☐	
Have you had changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness?	Yes ☐	No ☐	
Have you felt cold?	Yes ☐	No ☐	
Have you gained or lost weight?	Yes ☐	No ☐	
Have you had hair loss?	Yes ☐	No ☐	
Has your voice gotten deeper?	Yes ☐	No ☐	
Have you noticed your skin or eyes turning yellow?	Yes ☐	No ☐	
Are you experiencing increased thirst?	Yes ☐	No ☐	
Are you urinating more or less often than usual?	Yes ☐	No ☐	
Is your urine bloody, dark, or tea-colored?	Yes ☐	No ☐	
Do you bleed or bruise more easily than normal?	Yes ☐	No ☐	
Do you have swelling in your ankles?	Yes ☐	No ☐	
Have you had severe or constant muscle or joint pain?	Yes ☐	No ☐	
Have you had severe muscle weakness?	Yes ☐	No ☐	
Have you been running a fever?	Yes ☐	No ☐	
Have you had changes in your eyesight?	Yes ☐	No ☐	
Have you started taking any new medications (prescription, nonprescription, or herbal)? If yes, which and how often?	Yes ☐	No ☐	
Have you experienced any weakness?	Yes ☐	No ☐	
PULMONARY			
Do you have a new cough or one that has worsened?	Yes ☐	No ☐	
Are you having chest pain?	Yes ☐	No ☐	
Are you having trouble breathing or shortness of breath?	Yes ☐	No ☐	
GASTROINTESTINAL			
Are you severely nauseous and/or vomiting?	Yes ☐	No ☐	
Do you have a loss of appetite or have you felt less hungry than usual?	Yes ☐	No ☐	
How many bowel movements are you having each day?			
• Is this different than normal? If yes, how?	Yes ☐	No ☐	
• Are your stools loose or watery, or do they have a foul smell?	Yes ☐	No ☐	
• Have you seen blood or mucous in your stools?	Yes ☐	No ☐	
• Are your stools dark, tarry, or sticky?	Yes ☐	No ☐	
Are you having painful bowel movements?	Yes ☐	No ☐	
Are you having pain or tenderness around your belly? If yes, where?	Yes ☐	No ☐	

Checkpoint inhibitors | *Summary of irAEs*

ORGAN	FREQUENCY (all grades /severe)	TIMING	MANAGEMENT (mild / moderate / severe)
Skin	33% / <3%	weeks	Topical steroids / oral systemic steroids / IV methylpred
GI - colitis	33% / <7% or 1%	weeks	Loperamide / IV methylpred + consider infliximab
GI- hepatitis	<9% or <2%	weeks	Monitor / oral steroids / oral or IV steroids + consider MMF
Endocrine (hypothalamus, thyroid)	<5%	months	Hypothyroid: levothyroxine Hypophysitis: methylpred/pred, indefinite hormone replacement
Lung	5% / <1%	Median 2.5 months	Monitor / methylpred + consider infliximab with slow steroid taper
Kidney	2%	Median 3 months	Monitor / pred / methylpred + consider infliximab, aza, MMF with slow taper
Eye (uveitis)	variable	variable	Artificial tears / ophthalmic steroid / + systemic steroid with slow taper
CNS	5% / < 1%	Median 6 weeks	Depends on specific condition
CV - myocarditis	1%	Median 4 weeks	If severe, methylpred + consider infliximab with slow taper
MSK - arthralgia	variable	variable	NSAID / pred / methyl pred + consider infliximab with slow taper

~ for additional detail, see nccn.org ~

Checkpoint inhibitors | *Adverse effects*

What are the most common side effects? And what are the side effects that are unique to checkpoint inhibitors?

Like chemotherapy, fatigue, n/v/d, rash, cytopenias.
Immune-related adverse events are unique:
Skin, GI/liver, Endocrine, Lung

When do these side effects typically develop?

Anytime; from weeks to months after start.

How do I manage immune-related adverse events?

Depends. In general, steroids/immunosuppression.
Enlist multidisciplinary support.

Summary

- New for oncologic emergencies:
  - Denosumab for hypercalcemia of malignancy
  - New therapies = new risks for TLS
  - Caplacizumab for TTP

- Adverse effects of checkpoint inhibitors
  - Although conventional side effects are more common, have a high degree of suspicion for immune-related adverse effects.
    - Most common: skin, GI, hepatic, endocrine, lung
    - Steroids and multidisciplinary care.
    - In most cases, CPI can be restarted with resolution of irAE