Managing Immune-Related Adverse Events: Learning from Case Studies

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Objectives

- Identification and management of irAEs
- Review current resources to support optimal patient management
- Consideration of Quality of Life on I-O

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Head & Neck Squamous Cell Carcinoma (HNSCC)

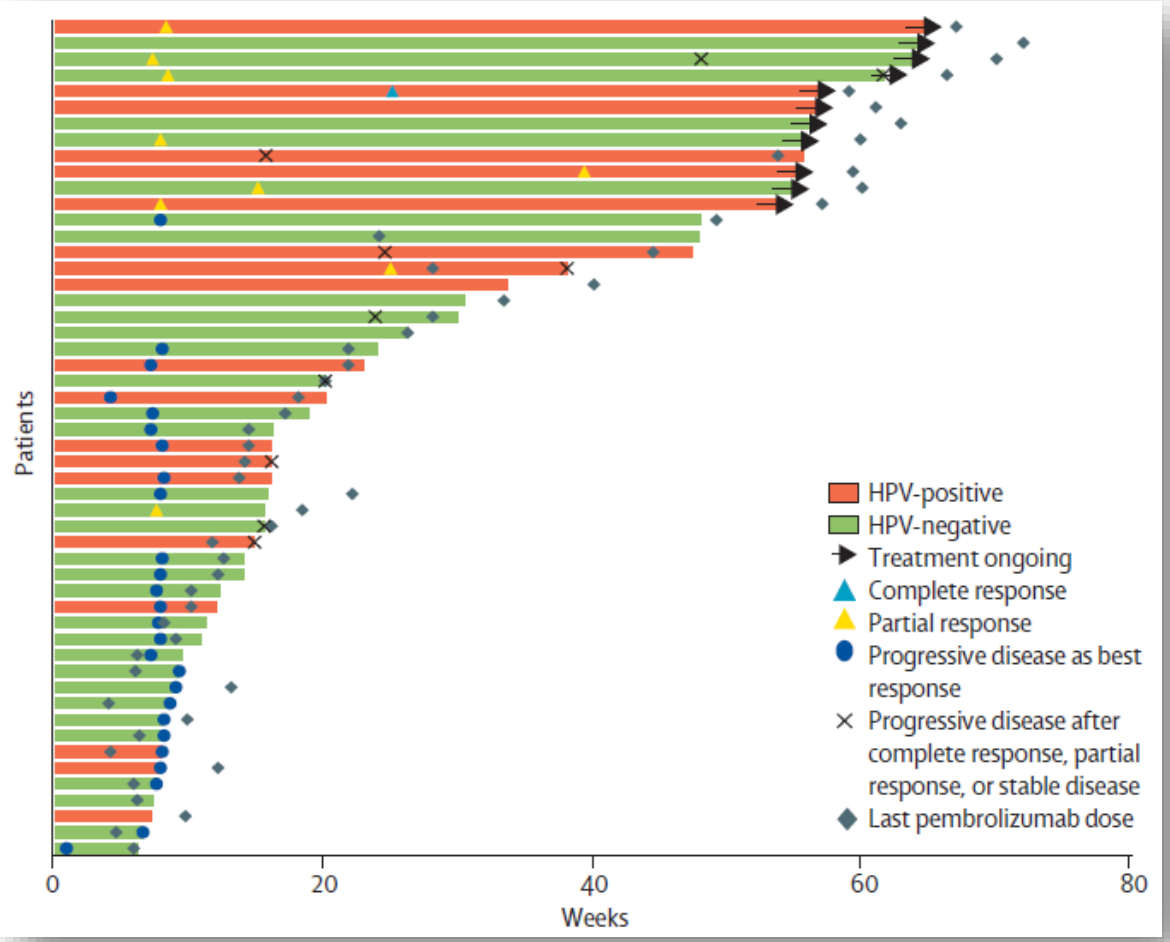
Approved Immunotherapy

- Pembrolizumab granted accelerated approval 8/5/2016 for HNSCC after progression beyond platinum-containing chemotherapy
  - Based on data from KEYNOTE-012
  - Confirmation study (KEYNOTE-040)
- FDA approved nivolumab 11/10/16 for the same indication as pembrolizumab
  - Based on data from CheckMate- 141

KEYNOTE-012

- Open-label, multicenter, phase Ib trial of patients with recurrent or metastatic HNSCC
- Inclusion: 18 or older, recurrent/metastatic HNSCC, any level of PD-L1 expression
- Treated with pembrolizumab 10 mg/kg every 2 weeks
- 18% overall response in all patients
  - 25% overall response in HPV+ patients
  - 14% overall response in HPV- patients

KEYNOTE-012

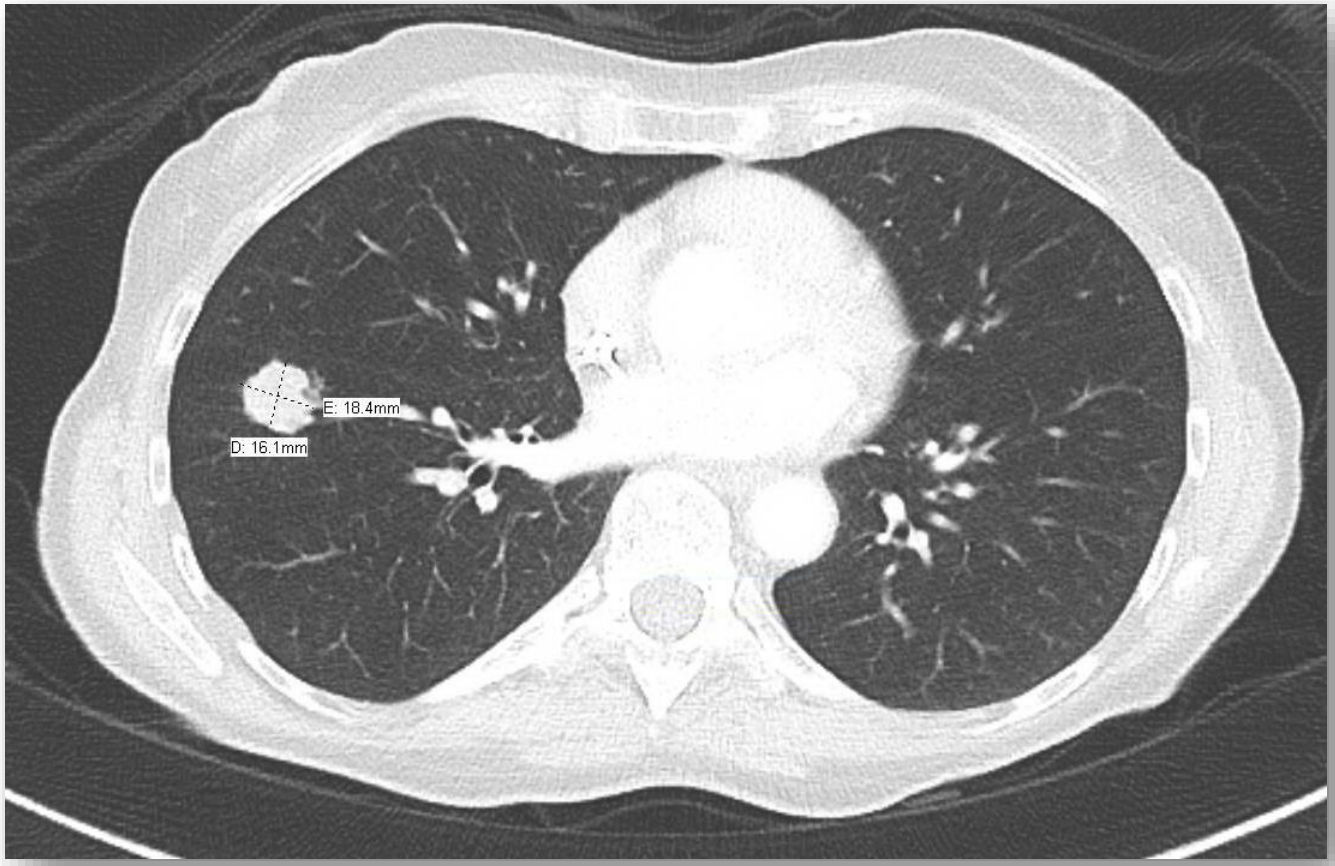


Seiwert TY, et al. *Lancet Oncol* 2016;17:956-65.

Case Study

- DC is a 65-year-old female with stage IVa (T2N2bM0) squamous cell carcinoma of the right tonsil
- Oncologic history
  - **10/20/2013:** R-sided tonsillectomy w/ pathology revealing poorly differentiated SCCa, HPV/P16+
  - **11/1/2013:** PET/CT FDG uptake in right tonsillar pillar (SUV 5.4), no cervical lymphadenopathy noted
  - **11/2013:** Right pharyngectomy and right lymph node dissection
  - Post-op treatment with XRT and weekly cisplatin, developed tinnitus and then on week 3 switched to carboplatin; tinnitus ultimately resolved
  - **3/11/2016:** CT chest revealing two separate round nodules; one in right lower lobe (1.8 x 1.5 cm) and another in left upper lobe (1.3 x 1.1 cm)
  - **3/14/2016:** PET/CT revealing left upper lobe and right lower lobe pulmonary nodules with intense associated increased uptake consistent with pulmonary metastatic disease, new since prior PET/CT; no evidence of local recurrence in pharyngeal soft tissues
  - **3/17/2016:** CT-guided biopsy of new PET positive lung nodules --> path: SCCa
  - **4/29/16-10/4/16:** Started EXTREME with 5-FU, carboplatin, and cetuximab, 5-FU stopped at cycle 2, carboplatin stopped at cycle 7
  - **11/14/16:** Started on pembrolizumab

Case Study (cont.)



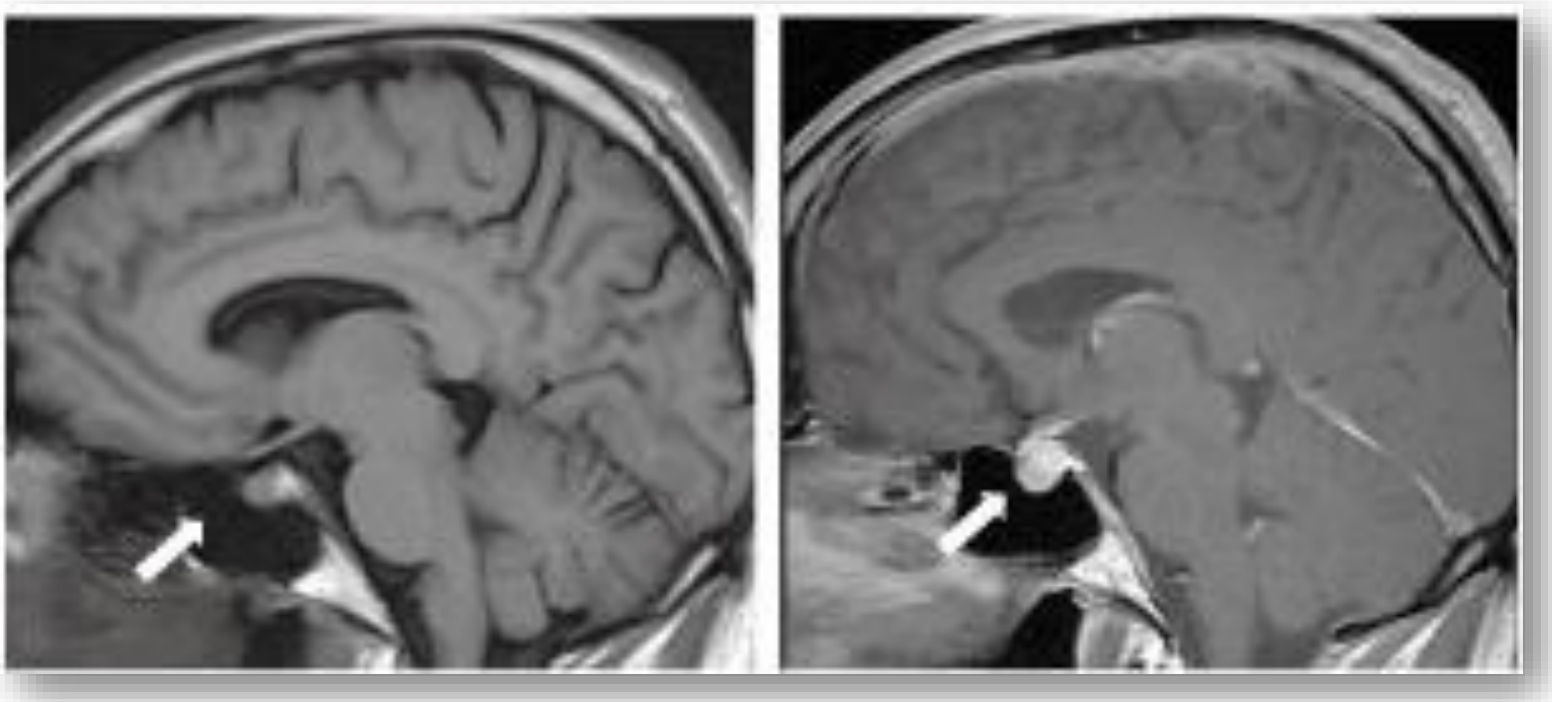
Right lung nodule prior to initiation of pembrolizumab (10/13/16)

Case Study (cont.)

- DC tolerating therapy well through the first 3 cycles
  - Mild joint pains controlled with 10 mg prednisone
- **1/20/17:** Presents for C4D1 pembrolizumab
  - Complains of headaches, dizziness, fatigue
  - Looks unwell
  - Obtain MRI brain with pituitary cuts
  - Check thyroid function

	ACTH (pg/mL)	TSH (ml/UL)	T4 (ng/dL)
Pre	30	1.3	1.1
Post	4	0.39	0.3
Reference	10-50	0.5-5.5	0.89-1.76

Case Study (cont.)



Pre-treatment

Prior to cycle 4

Grading irAE and Management

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					

Management

Overall Strategy:

- Ipilimumab to be withheld for any symptomatic hypophysitis (to be resumed when Grade 0/1 in those on ≤7.5 mg prednisone or equivalent per day), and discontinued for symptomatic reactions persisting ≥6 weeks or for inability to reduce steroid dose to ≤7.5 mg prednisone or equivalent per day
- Nivolumab to be withheld for Grade 2/3 hypophysitis and discontinued for Grade 4 hypophysitis. Pembrolizumab to be withheld for Grade 2 hypophysitis and withheld or discontinued for Grade 3/4 hypophysitis
- 1 mg/kg methylprednisolone (or equivalent) IV to be given daily
  - If given during acute phase, may reverse inflammatory process
- To be followed with prednisone 1-2 mg/kg daily with gradual tapering over 4 weeks
- Long-term supplementation of affected hormones is often required
  - Secondary hypothyroidism requiring levothyroxine replacement
  - Secondary hypoadrenalism requiring replacement hydrocortisone
    - Typical dose: 20 mg qAM and 10 mg qPM
- Patients may be weaned from steroid and replacement entirely over time
- Assess risk of opportunistic infection based on duration of steroid taper (and consider prophylaxis if needed)
- Collaborative management approach with endocrinology (particularly if permanent loss of organ function)

Case Study (cont.)

- Grade 2 hypophysitis
  - Prednisone 1mg/kg daily, taper over four weeks
- Grade 2 adrenal insufficiency due to hypophysitis
  - Initiated on hydrocortisone 20 mg every morning, 10 mg every evening
- Grade 2 hypothyroidism due to hypophysitis
  - Initiated on levothyroxine 100 µg orally daily
- OK to continue pembrolizumab once pred </= 10mg/day

Hypophysitis

- Inflammation of the pituitary resulting in low release of all or some of the following pituitary hormones[1]:
  - Adrenocorticotropic hormone (ACTH)
  - TSH
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
  - Growth hormone (prolactin)
- Symptoms[1]:
  - Headache
  - Fatigue
  - Muscle weakness
  - Constipation
  - Cognitive difficulties (related to thyrotropin axis)
  - Erectile dysfunction/amenorrhea (gonadotropin axis, LH/FSH)
  - Orthostatic hypotension, hypoglycemia/hyponatremia (corticotrophin deficiency, ACTH)

Hypophysitis

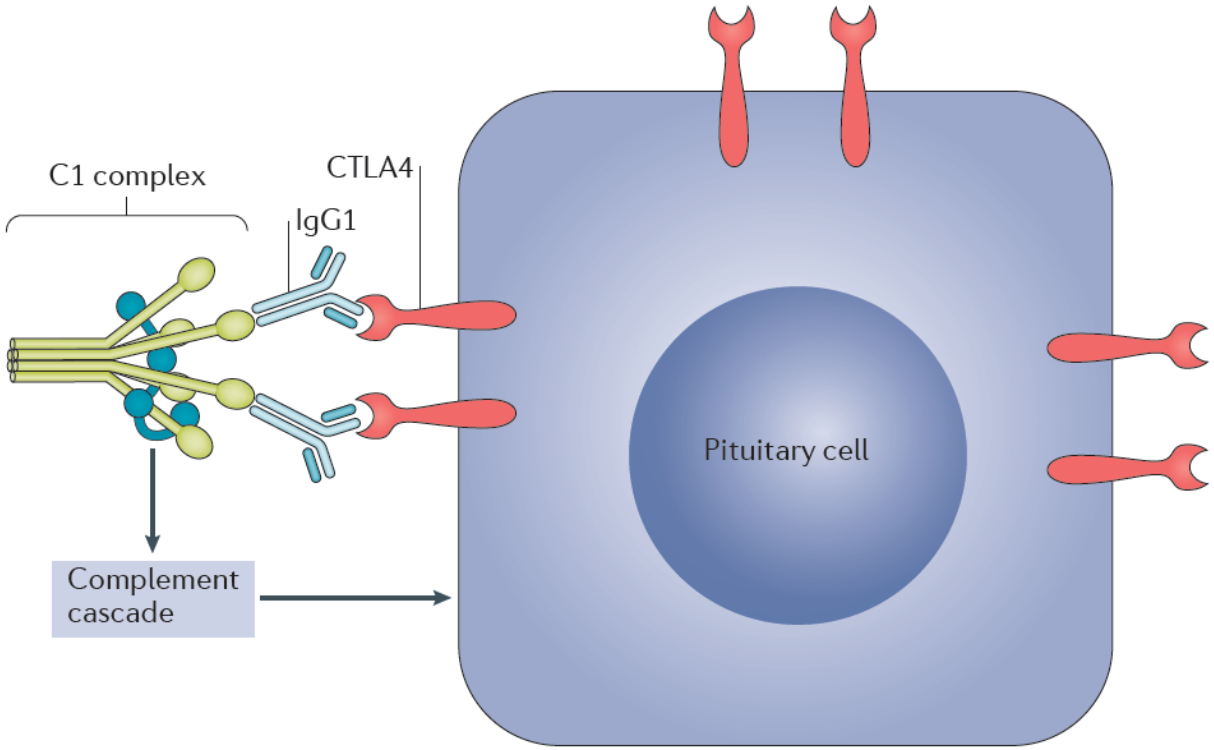


Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

1. Byun et al, Nature Reviews Endocrinology, 2017

Case Study (cont.)

- DC presents 4/14/17 for C8 pembrolizumab
  - Lethargic, tachycardic
  - Complains of severe thirst and frequent urination
  - Random glucose 524
  - Admitted for emergent management and workup

Care Step Pathway Type 1 Diabetes: Immune destruction of beta cells in pancreas

Nursing Assessment

Look:
- Does the patient appear fatigued?
- Does the patient appear dehydrated?
- Does the breath have a sweet/fruity smell?
- Is the patient tachycardic?

Listen:
- Frequent urination?
- Increased thirst?
- Increased hunger?
- Increased fatigue?
- Altered level of consciousness with advanced cases

Recognize:
- Symptoms of diabetes
- Serum glucose levels
- Other immune-related toxicity
- Infections

Grading Toxicity (Based on fasting glucose)

Grade 1 (Mild)
Fasting glucose value
> ULN – 160 mg/dL

Grade 2 (Moderate)
Fasting glucose value
> 160 – 250 mg/dL

Grade 3 (Severe)
Fasting glucose value >250 – 500 mg/dL, hospitalization indicated

Grade 4 (Potentially Life Threatening)
Fasting glucose value >500 mg/dL, life-threatening consequences

Grade 5: Death

Management (including anticipatory guidance)

Overall Strategy:
- Checkpoint inhibitors may be withheld until blood glucose is regulated
- Insulin therapy
- Hydration
- Endocrine consult

Nursing Implementation:
- Discuss that DM1 will likely be permanent
- Review signs symptoms of hyper/hypoglycemia
- Follow patients closely with checks on blood glucose levels, fruity breath, other symptoms, increased infections
- Assure early intervention is made
- Provide Insulin education (or refer for)
- Discuss possibility of other irAE including endocrine irAE

Diabetes Mellitus

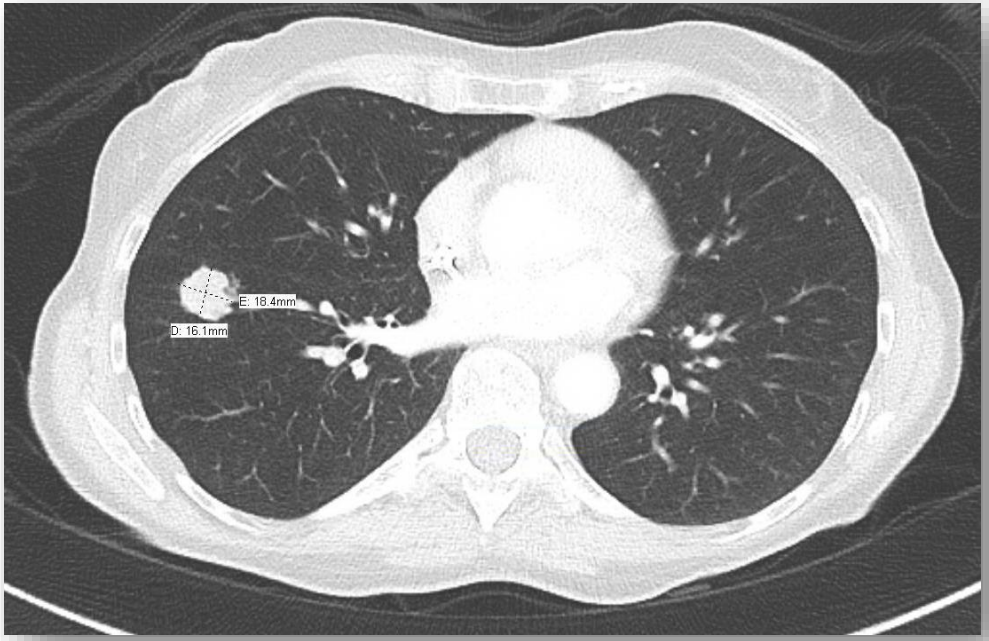
- Rare occurrence with PD-1
- Patients generally present in DKA[1]
- Work up should include testing for glutamic acid decarboxylase 65 (GAD65) antibodies
- Mechanism unclear[1]
  - In one study, 2 of 5 patients presented with upregulation of CD8+ T cell response to a T1DM antigen
  - 3 of 5 patients were found to have GAD65 antibodies
- Treatment with insulin therapy

1. Byun et al. *Nature Reviews Endocrinology*, 2017

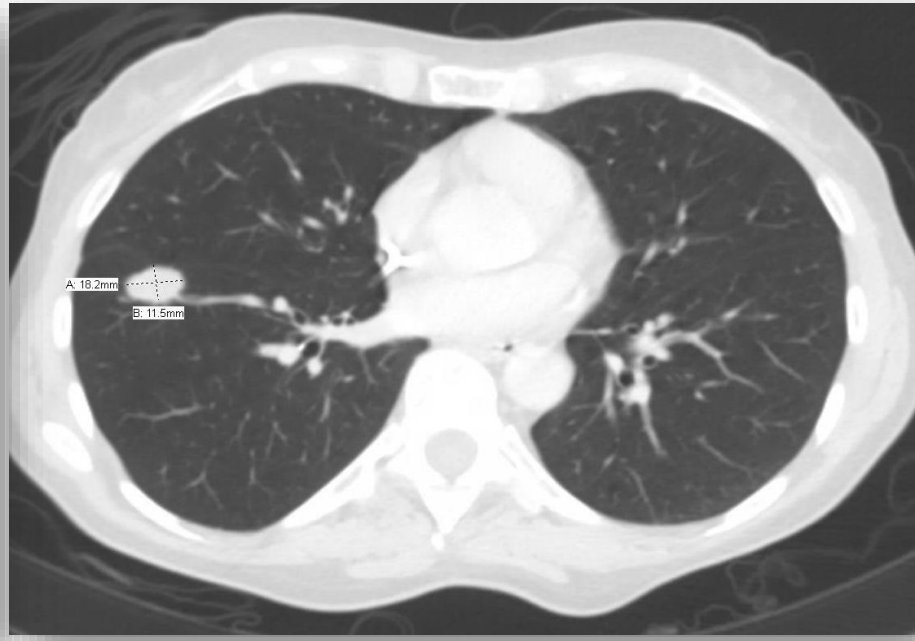
Case Study (cont.)

- Glutamic acid decarboxylase 65 (GAD65) antibodies positive
- DC diagnosed with new-onset DM1 secondary to pembrolizumab
- Pembrolizumab discontinued
- DC initiated on lifelong insulin therapy

Case Study (cont.)



Baseline



After 7 cycles of pembrolizumab

Urothelial Carcinoma

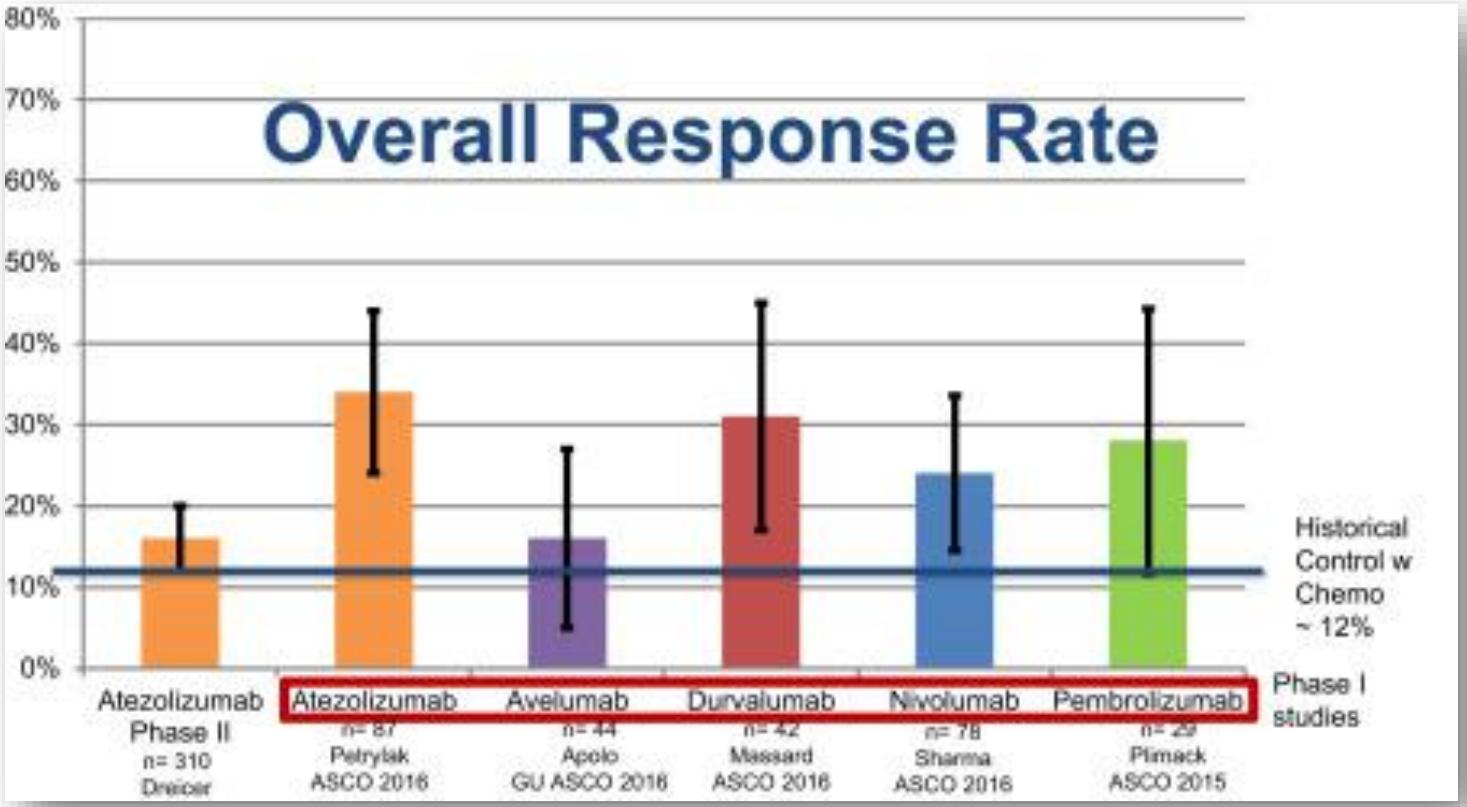
Approved Immunotherapy

- 2/2/17: Nivolumab
  - locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy
- 5/1/17: Durvalumab
  - Same indication
  - Also approved VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc.) as a complementary diagnostic for the assessment of the PD-L1 protein

Approved Immunotherapy

- 4/18/17: Atezolizumab
  - First line treatment for patients not eligible for cisplatin chemotherapy
- 5/9/17: Avelumab
  - Same indication
- 5/18/17: Pembrolizumab
  - Same indication
  - Also approved for those not eligible for cisplatin containing chemotherapy

Response Rates and Overall Survival of PD-1 Pathway Agents Compared with Chemotherapy Historical Control



Zibelman, MD, et al. *Urol Oncol* 2016;34:538-47.

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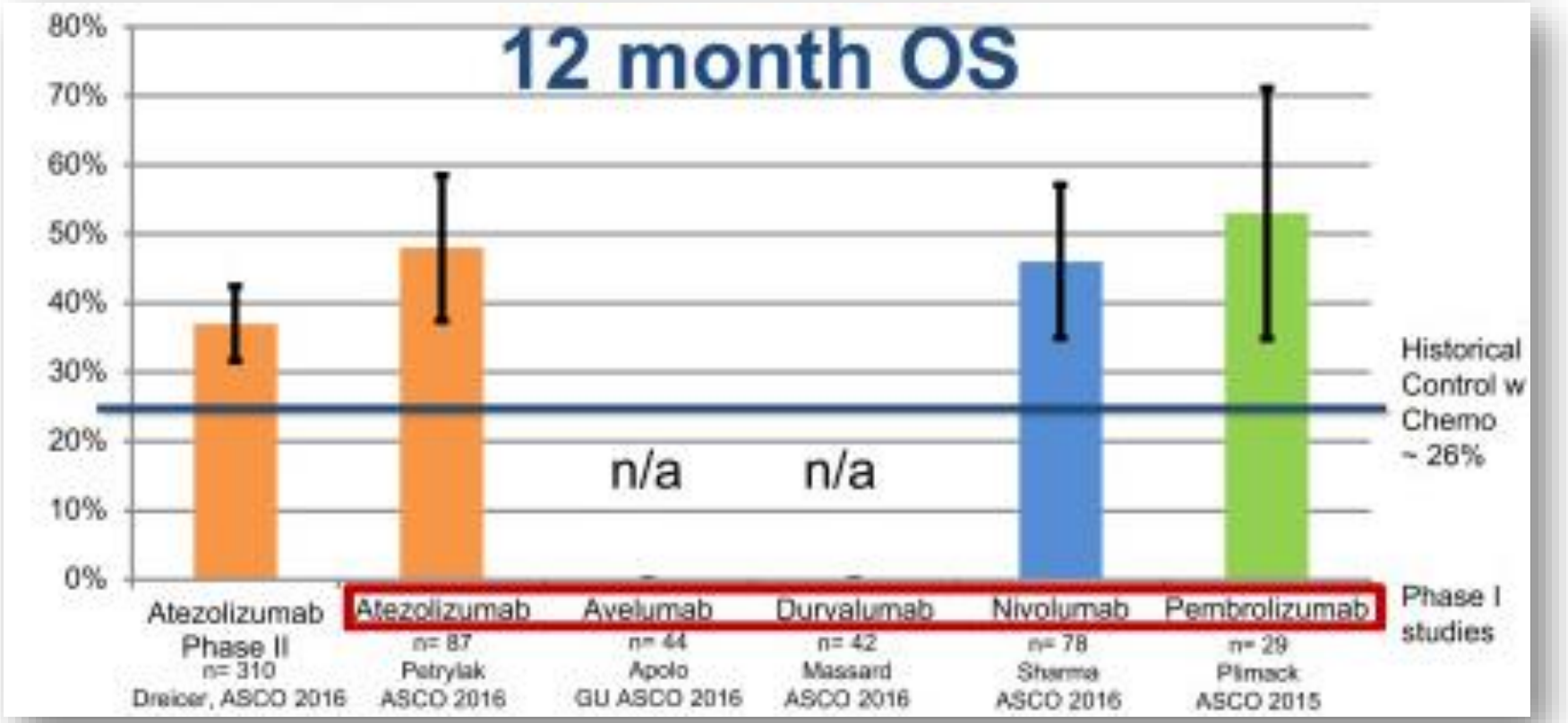


Zibelman MD et al. *Urol Oncol* 2016;34:538-47.

Case Study

- BR is a 67-year-old man diagnosed with metastatic urothelial cancer that progressed on platinum-based therapy
- Treated with atezolizumab 1200 mg IV every 3 weeks
- Imaging after four cycles showed stable disease
- Presents to clinic for cycle 6
  - Reports malaise and nausea
  - Denies taking NSAIDs or nephrotoxic medications
  - No history of hypertension, diabetes, or family kidney disease
  - Labs: Cr 4.5 (Baseline 1.9)

Differential Diagnosis

- Dehydration
- Infection
- Hydroureteronephrosis
- Disease progression
- Hypercalcemia of malignancy
- Nephritis

Further Workup

- UA
  - pH 6
  - Specific gravity 1.005
  - Blood small
  - Nitrites negative
  - Leuk esterase: 3+
  - WBC 38
  - RBCs 4
  - Protein: 1+
  - Eosinophils: No
- FE_{Na} >1%
- Urine culture: negative

Nephritis: Signs and Symptoms

- Elevated serum creatinine
- Elevated serum BUN
- Decreased creatinine clearance
- Electrolyte imbalance
- Decreased urine output
- Proteinuria
- Hematuria
- Peripheral edema
- Urinary eosinophils
- Urinary WBCs
- FENa >1%

The most typical clinical presentation is a sudden impairment of renal function associated with mild proteinuria and abnormal urinalysis for a patient with normal blood pressure and no edema.

Nephritis

- Seen in approximately 1% of patients on checkpoint inhibitor therapy[1]
- Includes:
  - Interstitial nephritis with inflammatory cortical renal enlargement
  - Granulomatous nephritis
  - Glomerular lupus-like nephropathy
- Median time to onset variable (6-30 weeks)[2]
- Diagnosis to include renal biopsy if needed
- Majority of patients recover renal function with steroids
- Recovery of renal function takes weeks

1. Michot et al, European Journal of Cancer, 2016;
2. Eigentler et al, Cancer Treatment Reviews, 2016

Renal Adverse Effects

Grading Toxicity

Acute Kidney Injury, Elevated Creatinine

Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal, renal, and post-renal.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Creatinine level >0.3 mg/dL; creatinine 1.5–2× ULN	Creatinine 2–3× ULN	Creatinine >3× ULN or > 4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	

- Creatinine 4.5 → Grade 3

Nursing Implementation:

- Identify individuals with pre-existing renal dysfunction prior to initiating immunotherapy. Ensure baseline creatinine has been obtained
- Check kidney function prior to each dose of immunotherapy
- Monitor creatinine more frequently if levels appear to be rising, and for Grade 1 toxicity
- Educate patients that new urinary symptoms should be reported immediately
- Anticipate the steroid requirements to manage immune-mediated nephritis are high (up to 1–2 mg/kg/d) and patients will be on corticosteroid therapy for at least 1 month
- Educate patients and family about the rationale for discontinuation of immunotherapy in patients who develop severe nephritis

RED FLAGS:

- **Risk of acute onset**
- **Risk of mortality if unrecognized or treatment is delayed**
- **Risk of immune-mediated nephritis is greater in patients receiving combination immunotherapy regimens and PD-1 inhibitors**
- **In addition to acute interstitial nephritis seen from PD-1 inhibitors, there are case reports of lupus-like nephritis and granulomatous acute interstitial nephritis**

Renal Adverse Effects

Management

Overall Strategy

- Assess for other etiologies, such as infection
- Eliminate potentially nephrotoxic medications
- Ensure adequate hydration daily
- Evaluate for progressive kidney/adrenal/pelvic metastases that may be contributing to kidney dysfunction
- Early intervention to maintain or improve physical function and impact on QOL

Mild elevation in creatinine (Grade 1)

- Anticipate immunotherapy to continue
- Perform detailed review of concomitant medications (prescribed and OTC), herbals, vitamins, anticipating possible discontinuation of nephrotoxic agents
- Avoid/minimize addition of nephrotoxic agents, such as contrast media for radiology tests
- Anticipate close monitoring of creatinine (i.e., weekly)
- Educate patient/family on importance of adequate daily hydration and set individualized hydration goals
- Review symptoms to watch for with patient and family and remember to assess at subsequent visits

Moderate elevation in creatinine (Grade 2)

- Ipilimumab to be withheld for any Grade 2 event (until Grade 0/1) and discontinued for events persisting ≥6 weeks or inability to reduce steroid dose to 7.5 mg prednisone/day
- Pembrolizumab or nivolumab to be withheld for Grade 2 events persisting ≥12 weeks or inability to reduce steroid dose to ≤10 mg prednisone or equivalent per day
- Anticipate increase in frequency of creatinine monitoring (i.e., every 2–3 days until improvement)
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Systemic corticosteroids (e.g., prednisone) 0.5–1 mg/kg/day until symptom improve to baseline followed by slow taper over at least 1 month
  - Anticipate increased in corticosteroid dosing (i.e., treat as if Grade 3 nephritis) if creatinine does not improve within 48–72 hours
  - Anticipate use of additional supportive care medications
- Upon symptoms resolution to patient's baseline, or Grade 1, begin to taper corticosteroid dose slowly over 1 month
- Anticipatory guidance on proper administration
- Anticipate the use of IV fluid to ensure adequate hydration
- Anticipate that nephrology consultation may be initiated by provider
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Moderate (Grade 3) and Severe (Grade 4)

- Pembrolizumab or nivolumab to be withheld for first-occurrence Grade 3/4 event and discontinued if:
  - Grade 3/4 event recurs
  - Persists ≥12 weeks
  - Requires >10 mg prednisone or equivalent per day for more than 12 weeks.
- Ipilimumab to be discontinued for any Grade 3/4 event
- Immunosuppressive medications to be initiated to treat immune-mediated nephritis
  - Corticosteroids (e.g., prednisone 1–2 mg/kg/day, in divided doses) until symptoms improve to baseline and then slow taper over at least 1 month
  - If symptoms do not improve within 48–72 hours, additional immunosuppressive medications will be considered
- Anticipate nephrology consultation will be initiated by provider
- Anticipate that renal biopsy will be considered
- Hemodialysis may be considered
- Anticipate possible hospital admission for Grade 4 elevations in creatinine or in patients with multiple comorbidities

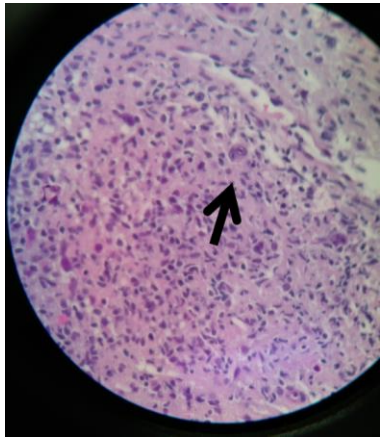
Case Study

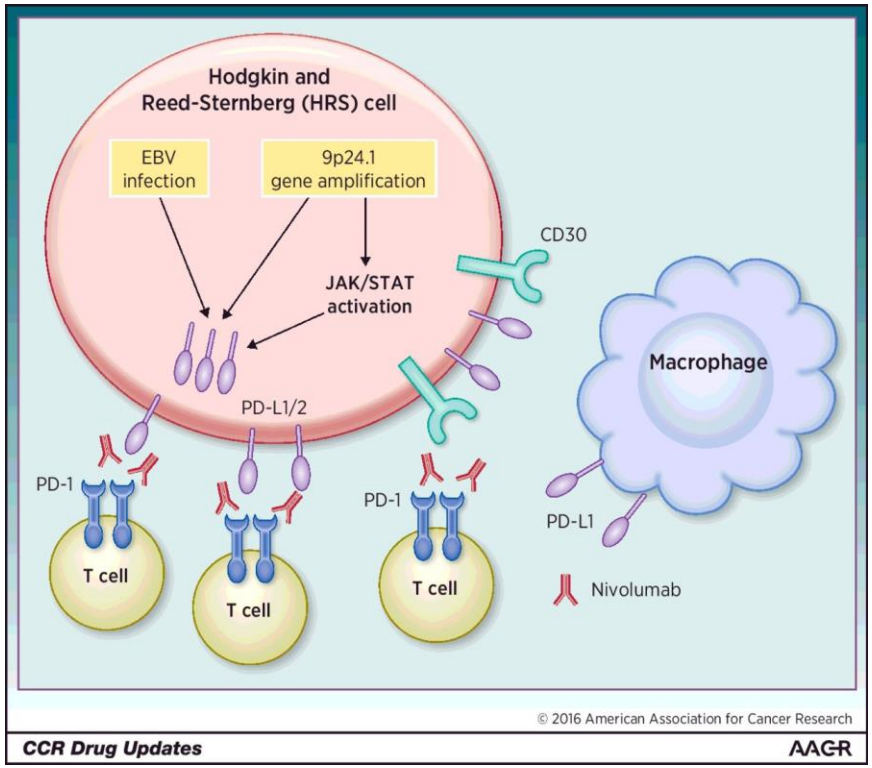
- BR was treated with prednisone 1 mg/kg for a month, and serial Cr was measured 2x per week
- His renal function recovered after 4 weeks, and the steroids were tapered over the next 8 weeks
- He was treated with sulfamethoxazole and trimethoprim for PCP prophylaxis and clotrimazole troches for thrush prevention

Hodgkin Lymphoma

Hodgkin Lymphoma - Ineffective Immune Response

Extensive immune infiltrate recruited to the tumor by malignant Reed-Sternberg cells





Reed–Sternberg cells, Hodgkin cells, and intratumoral macrophages have increased expression of PD-L1 and PD-L2

- Genetic alterations at chromosome 9p24.1
- Epstein–Barr virus infection

Ineffective antitumor immune response partially due to PD-1 signaling that induces tolerance

Boyiadzis M, et al. *J Immunother Cancer* 2016;4:90; Ansell SM. *Clin Cancer Res* 2017;23:1623-6

Approved Immunotherapy

- Nivolumab approved 5/17/16
  - Classical Hodgkin lymphoma that has relapsed or progressed after autologous HSCT and post-transplantation brentuximab vedotin
  - Or, 3 or more lines of systemic therapy that includes autologous HSCT
  - Nivolumab 3 mg/kg IV over 60 min every 2 weeks
- Pembrolizumab approved 3/14/17
  - Classical Hodgkin lymphoma that is refractory or has relapsed after 3 or more prior lines of therapy
  - Adults: Pembrolizumab 200 mg IV over 30 min every 3 weeks
  - Pediatrics: Pembrolizumab 2 mg/kg (up to 200 mg) IV over 30 min every 3 weeks

CheckMate 205: Nivolumab for Relapsed Hodgkin Lymphoma After HSCT and Brentuximab

	6-mo follow-up (n = 80)	12-mo follow-up (n = 80)
Objective response	66%	68%
Median duration of response	7.8 mo	13.1 mo
CR	8%	8%
Median duration of CR	4.6 mo	Not reached
PR	58%	60%
Median duration of PR	7.8 mo	13.1 mo
Median progression-free survival	10 mo	14.8 mo

Younes A, et al. *Lancet Oncol* 2016;17:1283-94; Timmerman J, et al. ASH 2016. Abstract 1110.

Case Study

- 35 year-old-man with classic Hodgkin lymphoma
  - Autologous stem cell transplant 1/25/16
  - Brentuximab vedotin (Adcetris) 5/1/16-8/1/16
  - Relapsed disease noted on 8/1/16 scans
  - 8/8/16 initiated on nivolumab 3mg/kg Q2 weeks

Case Study (Cont)

- 10/3/16 patient presents for C5D1 complaining of fatigue, dyspepsia, abdominal pain and decreased appetite
  - Denies nausea, vomiting or diarrhea
  - No change in color of urine or stool
  - Low grade temperature (100.1)

Case Study (Cont)

- Differential Diagnoses:
  - Anemia
  - Hepatitis
  - Hypothyroidism
  - Hypophysitis
  - Pancreatitis
  - Disease progression
  - Poor sleep quality
  - Infection

Case Study (Cont)

- Labs 10/3/16:
  - **Hgb:** 10.5 (*12.1-16.3 g/dL*) (baseline Hgb 10.9)
  - **LDH:** 261 (*124-271 U/L*)
  - **TSH: 4**.4 (*0.34-5.6 mIU/L*)
  - **T3:** 2.7 (*2.3-4.2 pg/ml*)
  - **T4:** 1.53 (*0.89-1.76 ng/dL*)
  - **AST:** 121 *(12-39 U/L)*
  - **ALT:** 170 *(7-52 U/L)*
  - **Tbili:** 1.9 *(0.1-1.3 mg/dL)*
  - **Alk Phos:** 105 *(39-117 U/L)*

Hepatitis

Grading Toxicity: ULN

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
AST/ALT: >ULN – 3.0× ULN	AST/ALT: >3.0× – 5.0× ULN	AST/ALT: >5.0× – 20.0× ULN	AST/ALT: >20× ULN	
Bilirubin: >ULN – 1.5× ULN	Bilirubin: >1.5× – 3.0× ULN	Bilirubin: >3.0× ULN	Bilirubin: >10× ULN	

Nursing Implementation:

- Review LFT results prior to administration of immunotherapy
- Early identification and evaluation of patient symptoms
- Early intervention with lab work and office visit if hepatotoxicity is suspected
- Grade LFTs and any other accompanying symptoms

RED FLAGS:

- **Severe abdominal pain, ascites, somnolence, jaundice, mental status changes**

Hepatitis

Management (including anticipatory guidance)

Overall Strategy:

- LFTs should be checked and results reviewed prior to each dose of immunotherapy
- Rule out infectious, non-infectious, and malignant causes. Consider assessing for new onset or re-activation of viral hepatitis, medications (acetaminophen, statins, and other hepatotoxic meds, or supplements/herbals), recreational substances (alcohol); consider disease progression

Infliximab infusions <u>are not</u> recommended due to potential hepatotoxic effects

Grade 1 (Mild)

- Immunotherapy may be withheld if LFTs are trending upward; recheck LFTs within ~ 1 week

Grade 2 (Moderate)

- Immunotherapy to be withheld; recheck LFTs daily x 3 days or every 3 days; to be resumed when complete/partial resolution of adverse reaction (Grade 0/1)
- Immunotherapy to be discontinued for Grade 2 events lasting ≥6 (ipilimumab) or ≥12 weeks (pembrolizumab, nivolumab), or for inability to reduce steroid dose to 7.5 mg prednisone or equivalent per day
- Consider starting steroids* 0.5 mg – 1 mg/kg/day prednisone or equivalent daily (IV methylprednisolone 125 mg total daily dose) + an anti-acid
- Consider hospital admission for IV steroids*
- If LFT normalized and symptoms resolved, steroids* to be tapered over ≥ 4 weeks when function recovers
- Once patient returns to baseline or Grade 0-1, consider resuming treatment

Grade 3 (Severe)

- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily oral
- Nivolumab to be withheld for first-occurrence Grade 3 event. Ipilimumab to be discontinued for any Grade 3 event, and nivolumab or pembrolizumab for any recurrent Grade 3 event or Grade 3 event persisting ≥12 weeks
- Admission for IV steroids*
- R/O hepatitis infection (acute infection or reactivation)
- Daily LFTs
- If sustained elevation is significant and/or refractory to steroids* potential for ADDING to steroid regimen immunosuppressive agent:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFT normalized and symptoms resolved, steroids* to be tapered over ≥4 weeks

Grade 4 (Life-Threatening)

- Immunotherapy to be discontinued
- Hospital admission
- Steroids* to be initiated at 2 mg/kg/day prednisone or equivalent daily intravenous
- R/O hepatitis infection
- Daily LFTs
- If sustained elevation and refractory to steroids* potential for ADDING to steroid regimen:
  - CellCept® (mycophenolate mofetil) 500 mg - 1000 mg po or IV q 12 hours OR
  - Antithymocyte globulin infusion
- Hepatology/gastroenterology consult
- Consider liver biopsy
- If LFTs stable/declining daily for 5 consecutive days: decrease LFT checks to q 3 days, then weekly
- If LFTs normalized and symptoms resolved, steroids* to be tapered slowly over ≥4 weeks

Hepatitis

- Incidence
  - Less common than colitis, seen in 2 to 9% of patients and at least 1 death has been reported on anti-CLTA-4 therapy alone[1]
  - Incidence with anti-PD-1 closer to 0.5%[2]
  - Hepatotoxicity appears worse when ipilimumab combined other drugs including dacarbazine[3] and vemurafenib[4],
  - Combination therapy 15-18% overall and 6-8% grade 3-4[5]
- Time to onset 8-12 weeks in single agent, sooner in combination[6]

1. Hodi et al, NEJM, 2010; 2. Pembrolizumab PI; 3. Robert et al, NEJM, 2011; 4, Ribas et al, NEJM, 2013; 5. Larkin et al, NEJM, 2015; 6. Friedman et al, JAMA Oncology Review, 2016

Case Study (Cont)

- Grade 2 Hepatitis
  - Initiate prednisone 1mg/kg daily
  - Hold immunotherapy
  - Start PPI
  - Check LFT daily x 3 days, then at least weekly
  - Taper steroid over four weeks
  - OK to continue treatment with nivolumab once prednisone </= 10mg per day and LFT Grade 0 or 1

I-O and Quality of Life

HNSCC QOL

- CheckMate 141 Study:
  - Nivolumab versus single agent therapy of investigator's choice in recurrent or metastatic HNSCC
  - Evaluation using EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D-3L
- Results:
  - Improved or stable quality of life (QOL) scores following treatment with single-agent nivolumab
  - Patients assigned to investigator's choice of treatment saw clinical meaningful declines, defined as a decrease in ≥10% from baseline, across 8 of 15 (53%) domains on the EORTC QLQ-C30 questionnaire

Harrington, K.J., et al. Lancet Oncol, 2017.

HNSCC QOL (Cont)

- Nivolumab significantly delayed median time to deterioration compared with investigator's choice for pain, sensory problems, social contact problems, and mouth opening problems on the EORTC QLQ-H&N35 questionnaire.
- Patients in the nivolumab group reached median time to clinically meaningful increase in weight, but not in the investigator's choice group.

Harrington, K.J., et al. Lancet Oncol, 2017.

HNSCC QOL: Are we answering the question?

- Checkpoint inhibitors have a different side effect profile than chemo and therefore standard instruments may not address symptoms fully
  - i.e.: skin problems are not addressed in EORTC QLQ-H&N35, but rash and pruritus were noted more frequently in the nivolumab group than standard therapy
- Patients with advanced disease and poor QOL often drop out of study sooner than those with better QOL

Singer, S. Lancet Oncol, 2017.

Adjuvant Ipilimumab in Melanoma

- Adjuvant ipilimumab approved October 2015 at a dose of 10mg/kg based on EORTC 18071 showing overall survival benefit
- EORTC QLQ-C30 questionnaire utilized in this study was similar between ipilimumab and placebo groups
- Treatment was *discontinued in 50% of patients due to drug-related adverse events*

Lorigan & Green, Nature Reviews, 2017

I-O and QOL

- Current standardized tools may not be accurately measuring QOL in I-O
- Further QOL research is needed as the indications for I-O continue to grow

Future Directions

Rewriting Life

Immunotherapy Pioneer James Allison Has Unfinished Business with Cancer

Why do most patients fail to respond to the newest cures?

by Adam Piore April 24, 2017

R. KIKUO JOHNSON

Future Directions

"For every miracle cure, for every Jimmy Carter or 22-year-old melanoma patient pulled back from death, there are many more people who, for reasons that no one understands, can't be saved. Of all patients dying from all types of cancer in America this year, only one in 12 would be expected to benefit from any immunotherapy drug. Some even argue that direct-to-consumer marketing, including a Super Bowl ad, has created dangerous expectations. Patients cashing in their last chance will, more likely than not, find themselves among the large majority for whom drugs like Allison's don't yet work."

Thank you for participating in the ICLIO webinar. Presentation slides and archived recording will be available at accc-iclio.org.

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