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INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

Management of Immune-related Adverse Events (irAEs) in Patients with NSCLC

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Objectives

- Recognize and monitor for adverse events associated with approved checkpoint inhibitors in patients with metastatic non-small cell lung cancer
- Discuss adverse event profile associated with checkpoint inhibitor combination therapy
- Discuss the management of immune mediated adverse events in non-small cell lung cancer
- Case review and interpretation

Basis of Side Effects

- Immune checkpoint inhibitors promote T-cell activity
- Activation of the immune system cannot be confined to antitumor effects
- Amplification of immune system can cause T-cells to attack healthy tissue: “auto-immunity”
- Common side effects
  - fatigue, decreased appetite and arthralgia
- Immune-related adverse events (IrAEs)
  - Inflammation (-”itis” or “-opathy”)

General Adverse Events

Drug	Dose Schedule	Indication	Common Adverse Events (> 20%)
Pembrolizumab	200 mg IV q 3 weeks Over 30’	1. First line patients with high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%, with no EGFR or ALK tumor aberrations, and no prior systemic chemotherapy 2. Second line after disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK tumor aberrations should have disease progression on FDA-approved therapy. Tumors expressing PD-L1 (TPS>1%)	fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation and nausea
Nivolumab	240 mg IV q 2 weeks Over 60’	Second line after disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK tumor aberrations should have disease progression on FDA-approved therapy.	fatigue, rash, cough, decreased appetite, pruritus, diarrhea, myalgia, arthralgia
Atezolizumab	1200 mg IV q 3 weeks Over 60 ‘	Second line after disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK tumor aberrations should have disease progression on FDA-approved therapy.	Fatigue, decreased appetite, dyspnea, cough, nausea, musculoskeletal pain and constipation

Summary of Most Common irAEs

Immune Related Adverse Events	Pembrolizumab			Nivolumab			Atezolizumab		
	ALL N=2799	Gr 1-2	Gr 3-4	ALL N=1994	Gr 2	Gr 3-4	ALL N=1027	Gr 1-2	Gr 3-5
Pneumonitis	3.4%	2.1%	1.3%	3.1%	1.3%	1.1%	3.7%	(22)	(16)
Colitis Dirarrhea	1.7%	0.4%	1.2%	2.9%	1%	0.7%	0.5%	(4)	(1)
Rash	17%*		4.8%	9%		0.3%			
Hepatitis	0.7%	0.1%	0.5%	1.8%	1%	0.7%	0.9%	(4)	(5)
Nephritis	0.3%	0.1%	0.2%	1.2%	0.8%	0.3%			
Diabetes Mellitus	0.2%			0.9%		2-KA	0.3%		(3)
Hypothyroid	8.5%	6.2%	0.1%	9%	Levothyroxine 73%		4.2%	(40)	(3)
Hyperthyroid	3.4%	0.8%	0.1%	2.7%	Medical 26%		1.1%	(11)	
Hypophysitis	0.6%	0.2%	0.4%	0.6%	0.2%	0.1%	0		

Pembrolizumab

Safety Data in Metastatic NSCLC

- N=682
- Permanent Discontinuation: 8%
  - Most common AE: pneumonitis (1.8%)
- Treatment delay: 23%
  - Diarrhea (1%)
  - Fatigue (1.3%)
  - Pneumonia (1%)
  - Liver enzyme elevation (1.2%)
  - Decreased appetite (1.3%)
  - Pneumonitis (1%)

Nivolumab

Safety Data in Metastatic NSCLC

- N= 418
- Permanent discontinuation: 11%
- Treatment delayed: 28%
- Serious adverse events: 46%
- >2% of patients: pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure
- 7 deaths due to infection; 4 deaths pulmonary embolism; 1 death limbic encephalitis

Atezolizumab

Safety Data in Metastatic NSCLC

- N=142
- Permanent discontinuation: 4%
- Treatment delayed: 24%
- Serious adverse events: 37%
  - Pneumonia, dyspnea, pleural effusion, pyrexia and venous thromboembolism
- Grade 5 events: 6.3% (9 deaths)
  - Pulmonary embolism (2), Pneumonia (2), Pneumothorax, ulcer hemorrhage, cachexia due to dysphagia, myocardial infarction or large intestinal perforation

Combination

Nivolumab plus Ipilimumab in NSCLC

- CheckMate 012
- Chemotherapy naïve metastatic NSCLC

- Nivolumab 1 mg/kg every 2 weeks plus Ipilimumab 1 mg/kg every 6 weeks
- Nivolumab 3 mg/kg every 2 weeks plus Ipilimumab 1mg/kg every 12 weeks
- Nivolumab 3 mg/kg every 2 weeks plus Ipilimumab 1 mg/kg every 6 weeks

- Primary outcome to assess frequency of adverse events and serious adverse events

Combination

Nivolumab plus Ipilimumab in NSCLC

	Nivolumab 3 mg/kg every 2 weeks plus Ipilimumab 1 mg/kg every 12 weeks (N=38)			Nivolumab 3mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (N=39)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Any Event	17 (45%)	13 (34%)	1 (3%)	15 (38%)	11 (28%)	2 (5%)
Endocrine	3 (8%)	1 (3%)	0	6 (15%)	2 (5%)	0
Diarrhea/ colitis	7 (18%)	2 (5%)	0	7 (18%)	2 (5%)	0
Hepatic	1 (3%)	0	0	0	1 (3%)	1 (3%)
Pulmonary	2 (5%)	2 (5%)	0	1 (3%)	1 (3%)	0
Renal	1 (3%)	2 (5%)	0	3 (8%)	0	0
Skin	14 (37%)	1 (3%)	0	12 (31%)	2 (5%)	0
Lipase ⇧	3 (8%)	2 (5%)	1 (3%)	0	0	0
Diabetes	0	0	0	0	0	1 (3%)

Combination

Nivolumab plus Ipilimumab across Studies

Adverse Event	Nivolumab(N=1994)	Nivolumab & Ipilimumab (N=407)
Pneumonitis	3.1% (61)	6% (25)
Colitis	2.9% (58)	26% (107)
Hepatitis	1.8% (35)	13% (51)
Hypophysitis	0.6% (12)	9% (36)
Adrenal Insufficiency	1% (20)	5% (21)
Hypothryoidism	9% (171)	22% (89)
Hyperthyoidism	2.7% (54)	8% (34)
Nephritis	1.2% (23)	2.2% (9)
Skin	9% (171)	22.6%(92)

Combination

Carboplatin and Pemetrexed +/-Pembrolizumab (Keynote-021)

AE	Pembrolizumab plus chemotherapy (N=59)				Chemotherapy (N=62)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any	32 (54%)	18 (31%)	4 (7%)	1 (2%)	40 (65%)	12 (19%)	2 (3%)	2 (3%)
Rash	15 (25%)	1 (2%)	0	0	9 (15%)	0	0	0
Diarrhea	12 (20%)	0	0	0	6 (10%)	0	0	0
Hypothyroid	9 (15%)	0	0	0	3 (5%)	0	0	0
Hyperthyroid	5 (8%)	0	0	0	1 (2%)	0	0	0
Pneumonitis	2 (3%)	1 (2%)	0	0	0	0	0	0
ALT/AST	9/10 (17%)	1 (2%)	0	0	6 (10%)	1 (2%)	0	0
Creat	6 (10%)	0	0	0	4 (6%)	0	0	0

Combination

Nivolumab with Platinum-Based Doublet: Checkmate 012

Gemcitabine-Cisplatin; pemetrexed-Cisplatin; Paclitaxel-Carboplatin

Adverse Event	Nivolumab Single	Nivolumab Combination
Skin Toxicity	25%	36%
Gastrointestinal	12%	23%
Renal	0%	14%
Pulmonary	6%	13%

21% of patients discontinued treatment (10 of 12 occurred in nivolumab arm)

Most treatment related Aes in combination were attributed to chemotherapy (fatigue, nausea, decreased appetite

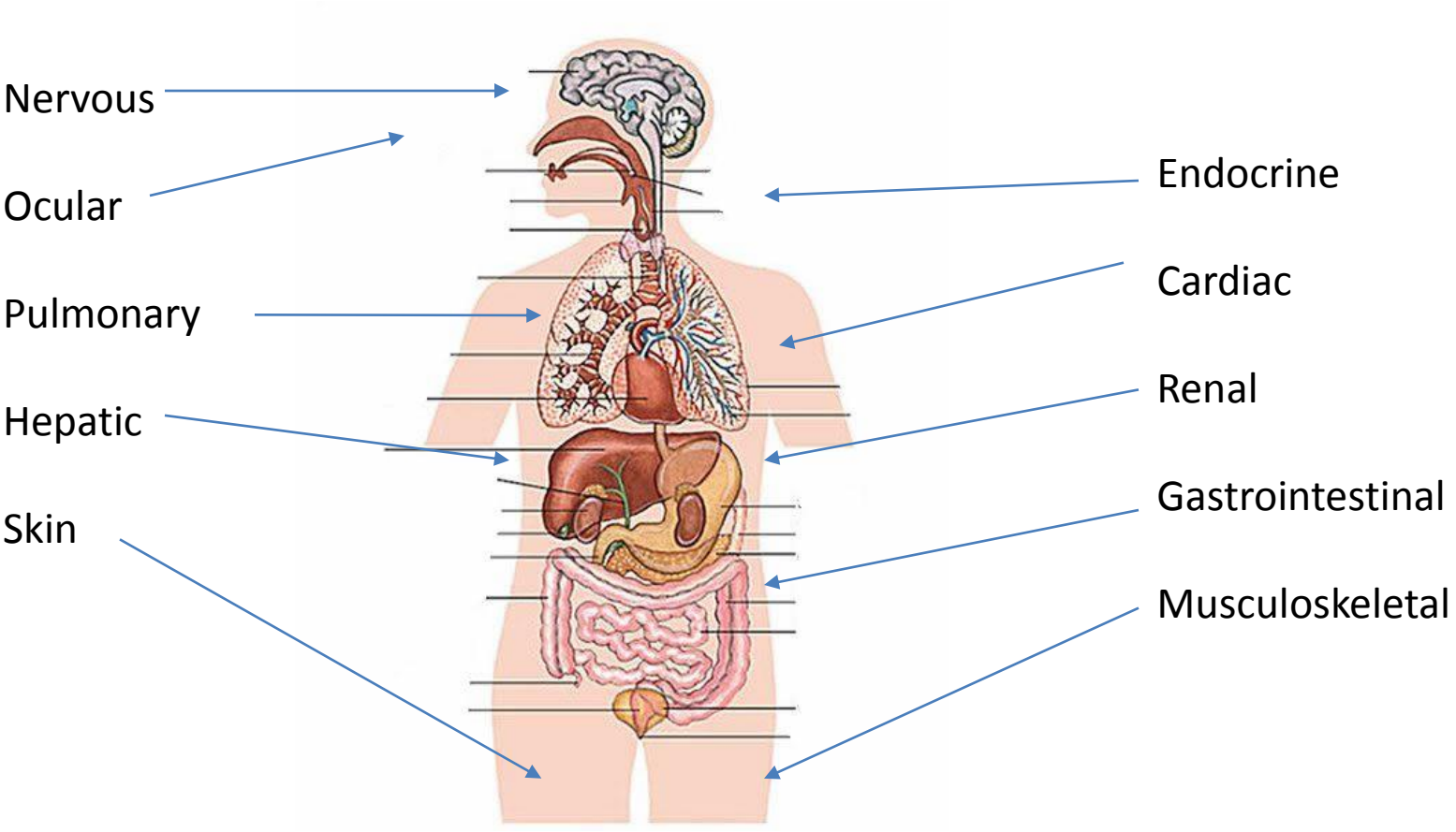
Pneumonitis increased in both, higher that chemotherapy alone. May be that steroid premedication held in nivolumab therapy

Patterns of Immune-Related Adverse Events

- Onset:
  - Median time to onset is 5-12 weeks after initiation of therapy
    - Within days of the first dose
    - After several months of treatment
    - After discontinuation of therapy
- May affect one or many organ systems
- Severity: Asymptomatic to severe & life threatening
- Suggested dose dependency
- Suggested cumulative effect
- Increased in combination with other immunotherapy agents, chemotherapy or radiation

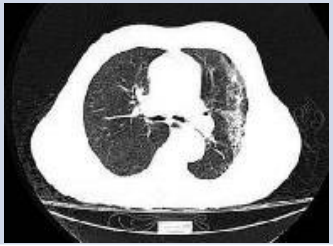
Immune-Related Adverse Events

By System



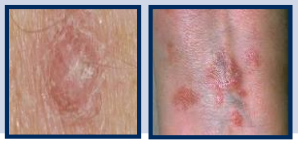
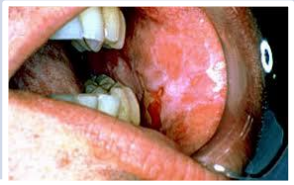
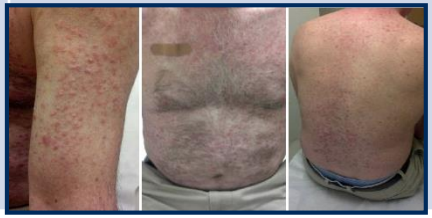
Pulmonary Toxicity

Pneumonitis, Respiratory Failure

Signs/Symptoms	Grading	Evaluation	Management
Onset: 2 days through therapy Dyspnea Dry cough, wheezing Tachypnea, tachycardia Shortness of breath at rest Hypoxia Increased oxygen requirements Chest pain Radiographic changes 	**Grade 1** • Asymptomatic: Clinical or diagnostic observations only. **Grade 2** • Mild-to-moderate symptoms, limiting instrumental ADL • Medical intervention indicated **Grade 3-4** • Severe symptoms; limiting self care ADL • New/worsening hypoxia • Life-threatening, urgent intervention indicated	Oxygen saturation with ambulation Computerized tomography scan Rule out: -infectious cause -lymphangitic spread -pulmonary embolism -pleural effusion Pulmonary consult Interventional Pulmonology -Bronchoscopy & biopsy Infectious disease consult	**Grade 1** (radiographic changes only): consider withholding checkpoint immunotherapy; monitor every 2-3 days **Grade 2** (mild to moderate; worsens from baseline): withhold checkpoint immunotherapy; administer steroid 1-2 mg/kg/day prednisone equivalent; Daily Monitoring **Grade 3-4** (severe symptoms; new or worsening hypoxia; life-threatening) Permanent discontinuation; 2-4 mg//kg/day prednisone equivalent Oxygen support Albuterol nebulizer IV/oral steroid

Dermatologic

Rash, Pruritus, Dermatitis, Vitiligo, Lichenoid Implants

Signs/Symptoms	Grading	Evaluation	Management
Onset: 1-25 months or post treatment Maculopapular rash Pruritus Vitiligo -Hair -Skin Peeling, blisters Oral ulcerations Eosinophilic Infiltrates Epidermal Spongiosis Lichenoid Deposits Stevens-Johnson syndrome  	**Grade 1-2** • Covers ≤30% of body surface area • May or may not be associated with symptoms of pruritus **Grade 3-4** • Covers >30% of body surface area • May or may not be associated with symptoms of pruritus • Limiting self care ADL • Life-threatening consequences 	Rule out other causes: -cellulitis -contact dermatitis -other drug reaction -sun exposure -radiation recall Dermatology evaluation and consider skin biopsy 	**Grade 1-2** (covers ≤30% BSA): topical steroids, anti-itch creams. If rash persists >1 week or interferes with activities of daily living, start moderate-potency steroid cream (triamcinolone 0.1%) **Grade 3-4** (>30% BSA): If serious with desquamation, discontinue checkpoint immunotherapy treatment and manage with methylprednisolone 0.5-1.0 mg/day IV Supportive care: Antihistamines, hydroxyzine

Gastrointestinal

Diarrhea, Enterocolitis, Perforation

Signs/Symptoms	Grading	Evaluation	Management
Onset: 3 days to 10 weeks; after several months; Earlier with combination therapy Abdominal pain Cramping Change in bowel habits Increase in ostomy output, mucous or blood in stool, incontinence Perforation: sepsis, peritoneal signs, ileus	**Grade 1** • <4 stools/day over baseline; asymptomatic **Grade 2** • 4-6 stools/day over baseline; IV fluids indicated <24 h; colitis with abdominal pain, blood in stool; no ADL interference **Grade 3** ≥7 stools/day over baseline; IV fluids 24 h; interferes with ADL, severe abdominal pain, peritoneal signs; Medical intervention indicated **Grade 4** • Life-threatening; perforation	Calculate frequency and volume of diarrhea Rule out infectious cause -Stool for WBC (r/o inflammation) -Stool for C & S, *Clostridium difficile* Abdominal ultrasound Abdominal CT scan Gastroenterology consult Endoscopy/colonoscopy	Grade 1: continue treatment Grade 2: withhold treatment until grade 1; discontinue if recurrent or if lasting >5 days, initiate steroids Grade 3: withhold treatment and initiate steroids Grade 4 diarrhea or colitis: permanently discontinue Supportive Care: -hydration -dietary changes -anti-emetics -anti-diarrhea -anti-spasmodics Refractory: immunosuppressants --Infliximab (IV)

Gastrointestinal Toxicity

Pancreatitis

Signs/Symptoms	Grading	Evaluation	Management
Abdominal pain Diarrhea Nausea	**Grade 1:** Amylase & Lipase: >ULN-1.5 x ULN **Grade 2** Amylase & Lipase: >1.5-2.0 x ULN Enzyme elevation only Radiographic changes **Grade 3:** Amylase & Lipase: >2.0-5.0 x ULN Severe pain Medical intervention needed **Grade 4** Amylase & Lipase>5.0 x ULN Life threatening Urgent intervention needed	Laboratory evaluation -Amylase -Lipase -Liver function test Abdominal ultrasound Endoscopy Abdominal CT scan	Grade 2/3 pancreatitis- hold Grade 3 elevation of amylase or lipase (> 2.0 ULN) 1-2 mg/kg IV methylprednisolone Grade 4 pancreatitis: permanent discontinuation

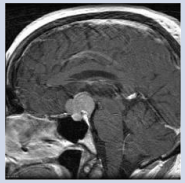
Endocrinopathies

Thyroiditis, Hyperthyroidism, Hypothyroidism

Signs/Symptoms	Evaluation	Management
Onset: 4-20 weeks Often asymptomatic Pattern: transient hyperthyroid followed by hypothyroid	Laboratory: TSH, free T4 (thyroxine), T3 (triiodothyronine), [low free T4 and high TSH] Endocrinology Consult	
Hyperthyroid: weight loss, irritability, palpitations, diarrhea, feeling hot		Withhold immunotherapy Manage symptoms Antithyroid: methimazole Beta blockers Re-initiate when symptoms controlled
Hypothyroid: fatigue, sluggishness, anorexia, weight gain, dry skin, constipation, feeling cold		Initiate levothyroxine -Adjust to maintain free T4 in mid-range Re-initiate I-O when symptom free

Endocrinopathies

Hypophysitis, Adrenalitis, Adrenal Insufficiency

Signs/Symptoms	Evaluation	Management
Hypophysis Visual disturbances, headaches, fatigue, weakness, confusion, hallucinations, memory loss, labile mood, insomnia, anorexia 	Hormone levels: ACTH, FSH, LH, prolactin, ADH, oxytocin, testosterone; r/o sepsis. Endocrinology consult Pituitary scan (may be enlarged 50%-100%) MRI of brain: r/o brain metastases Monitor for progression to adrenal insufficiency/crisis	Stress dose IV steroids with mineral corticoid if adrenal crisis; Hormone replacement Symptomatic: hold therapy and replete Grade 4: permanent discontinuation
Adrenalitis Fatigue, malaise, hypotension, vague gastrointestinal symptoms, weight loss, hypoglycemia •Adrenal insufficiency •Adrenal crisis	Morning cortisol, ACTH, cosyntropin stimulation test; aldosterone AM cortisol <3 µg/dL: adrenal insufficiency Primary: low cortisol, high ACTH (primary adrenal) Secondary: low cortisol, low ACTH (pituitary disease) Endocrinology consult	May require lifetime hormone replacement Stress dosing requirements Dexamethasone (not measured in cortisol assays Isotonic saline for sodium repletion Symptomatic: hold therapy

Endocrinopathies

Diabetes Mellitus

Signs/Symptoms	Grading	Evaluation	Management
Fatigue Frequency of urination Increased thirst Increased appetite Blurred vision Weight loss (Type 1) Peripheral neuropathy (Type 2)	**Grade 1:** Fasting glucose >ULN-160 mg/dL **Grade 2:** Fasting glucose value >160-250 mg/dL **Grade 3:** >250-500 mg/dL Hospitalization indicated **Grade 4:** > 500 mg/dL	Blood glucose monitoring (fasting) Hemoglobin A1C Oral Glucose Tolerance Testing (OGTT) Abdominal ultrasound Abdominal CT scan Endocrinology Consult	Type 1 Diabetes: Administer insulin **Grade** 3: Severe Hyperglycemia Withhold immunotherapy until metabolic control achieved Administer anti-hyperglycemics Grade 4: Permanent discontinuation

Case

- A.H. is a 68 yr old female treated with PD-1 checkpoint inhibitor. At 7th cycle develops grade 3 hypothyroidism.
- Fatigue (several naps/day), Anorexia
- TSH 8.45 (normal 0.4-4.0 mIU/L)
- Free T4 1.6 (normal 4.5 to 11.2 mcg/dL)

Case

1. Hold immunotherapy until toxicity improves to grade 1
2. Continue immune check point therapy. Start thyroid replacement
3. Permanent discontinuation as grade 3 toxicity
4. Hold until toxicity resolve and restart at dose reduction

Case

- AH started on levothyroxine 25 mcg po daily
- TSH and T4 levels monitored every 4 weeks
- Treatment on immune therapy continued
- At week 4
  - TSH improved to 6.3
  - T4 improved to 2.0
- Levothyroxine increased to 50 mcg po daily

Hepatotoxicity

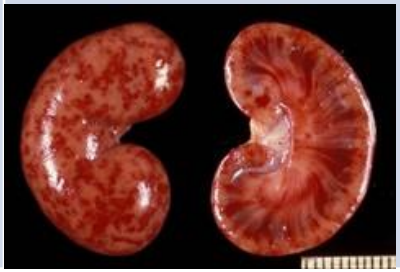
Transaminitis, Hepatitis

Signs/Symptoms	Grading	Evaluation	Management
Onset:: 9 days to months Nausea Fever Vague abdominal discomfort RUQ pain Dehydration Jaundice Bleeding, bruising Dark urine	**Grade 1** • AST or ALT >ULN to 3× ULN and/or total bilirubin >ULN to 1.5× ULN **Grade 2** • AST or ALT >3× to ≤5× ULN and/or total bilirubin >1.5× to 3× ULN **Grade 3-4** • AST or ALT >5× ULN and/or total bilirubin >3× ULN	Liver enzymes (AST, ALT, ALK, total and direct bilirubin) every 3 days Liver ultrasound Gastroenterology consult	Hold hepatic toxic drugs **Grade 1:** Continue treatment **Grade 2:** Withhold treatment; 0.5-1 mg/kg/day prednisone equivalent; If responds to grade 1, resume treatment when steroid tapered **Grade 3-4:** Permanently discontinue treatment; 1-2 mg/kg/day prednisone IV/oral steroid **Refractory** Mycophenolate

ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Nephrotoxicity

Nephritis, Renal insufficiency, Acute Renal Injury

Signs/Symptoms	Grading	Evaluation	Management
Onset: Days to months Often asymptomatic with increase in serum creatinine Vague: nausea, emesis Decreased urine output Cloudy/dark urine Blood in urine Ankle swelling	**Grade 1** • Creatinine level increase of >0.3 mg/dL; Creatinine 1.5-2.0 x above baseline **Grade 2** • Creatinine 2-3 x above baseline **Grade 3** • Creatinine >3 x baseline or > 4.0 mg/dL **Grade 4** Life-threatening	Serum creatinine, Urinalysis; Rule out: Hypovolemia Nephrology consult Renal ultrasound, biopsy 	Limit nephrotoxic medications Hydration **Grade 1**: Continue treatment **Grade 2-3:** Withhold treatment; monitor serum creatinine every 2-3 days; 0.5-1 mg/kg/day prednisone equivalent; if no improvement, increase to 1-2 mg/kg/day **Grade 4:** Permanently discontinue treatment; 1-2 mg/kg/day prednisone equivalent

Ocular Toxicities

Iritis, Uveitis, Conjunctivitis, Scleritis, Blepharitis

Signs/Symptoms	Grading	Evaluation	Management
Onset: days to months Painful, itchy watery eyes Decreased acuity Visual deficits Dry eyes Inflammation Injected conjunctiva	**Grade 1** • Asymptomatic or mild symptoms **Grade 2** • Symptoms limiting ADL • Anterior uveitis **Grade 3** •Symptoms limiting self-care •Posterior or pan-uveitis **Grade 4** • Perforation or blindness	Rule out infection Ophthalmology consult; slit lamp evaluation	**Grade 1**: Lubricating eye drops **Grade 2:** Topical; corticosteroid eye drops; may consider holding treatment **Grade 3**: Hold treatment; 0.5-1.0 mg/kg/day prednisone equivalent; may restart if decreased to grade 1 **Grade 4**: Permanent discontinuation; 1-2 mg/kg/day prednisone equivalent

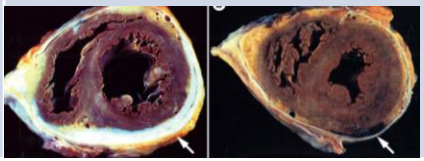
Neurologic Toxicities

Neuropathy, Meningitis, Guillain-Barre syndrome, Myasthenia Gravis, Temporal Arteritis

Signs/Symptoms	Grading	Evaluation	Management
Onset: 2 to 8 months Unusual weakness Numbness Difficulty walking Difficulty performing daily tasks (writing, dressing, feeding) Headache, confusion Memory difficulties Hallucinations Seizures	**Grade 1** • Asymptomatic or mild symptoms **Grade 2** • New-onset moderate symptoms limiting instrumental ADL **Grade 3-4** •New-onset severe symptoms limiting self-care • Life-threatening consequences	MRI of the brain Rule out: -Infection -Brain metastasis -Cerebral vascular accident Neurology consult	Grade 1: continue treatment Grade 2: Withhold treatment, initiate IV steroids (0.5-1.0 mg/kg/day) or oral equivalent Grade 3-4: Permanently discontinue treatment; 1-2 mg/kg/day steroids If worsens, consider other immunosuppressive therapy

Cardiac Toxicities

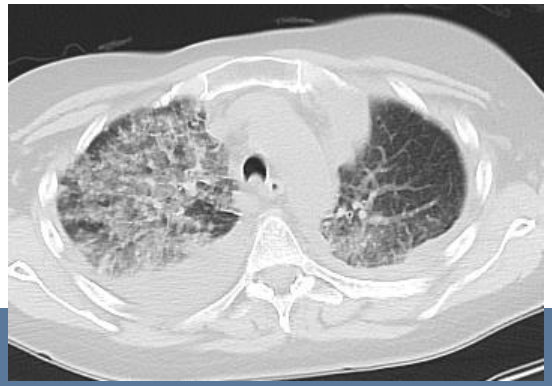
Pericarditis

Signs/Symptoms	Grading	Evaluation	Management
Onset: Days to months; After treatment completion Chest pain Dyspnea Fluid retention Pericarditis	**Grade 1** • Asymptomatic • Subtle ECG or physical findings (e.g., rub) **Grade 2** • Symptomatic pericarditis (e.g., chest pain) **Grade 3** •Symptomatic; pericarditis with physiologic consequences •Pain at rest **Grade 4** • Life-threatening consequences	ECG Echocardiogram CT Chest Cardiology consult 	**Grade 1**: Hold treatment **Grade 2:** Hold treatment until grade 1; medical intervention as indicated. 1-2 mg/kg/day prednisone equivalent **Grade 3-4:** Discontinue treatment; 2-4 mg/kg/day prednisone equivalent; medical intervention as indicated; IV steroids

Case #2

- S.G. is a 58-year-old male with NSCLC
- Status post 3 cycles of anti-CTLA-4 & anti-PD-1 (concurrent)
- History: “Sinusitis” x 1 week, unresponsive to antibiotics

- Presents for cycle 4 of treatment
  - Cough, chest tightness & shortness of breath
  - O_2 saturation: at baseline 98%; now 84% with ambulation
  - Chest x-ray: new infiltrate in left upper lobe of lung



Case

- Oxygen support with improved saturation
- CT Angiography:
  - Confirmed new ground glass opacity (GGO) & pneumonitis
  - Infection vs. drug induced pneumonitis
- Admission to hospital
  - I-O therapy held
- Bronchoscopy infiltrative pneumonitis

Case

- Methylprednisolone IV initiated at 1 mg/kg/d
- CT scan repeated at day 5 with improvement in opacities
- Methylprednisolone tapered to prednisone 60 mg po oral
- Discharged home when stable
  - Prednisone taper
  - Empiric voriconazole & sulfamethoxazole and trimethoprim

Algorithm for Management of irAEs

Grade	Assessment & Management
Grade 1	Asymptomatic; Diagnostic changes only; Continue immunotherapy
Grade 2	Mild to moderate symptoms; Grade 2 diagnostic abnormalities. Hold treatment. Provide supportive care. IV Steroid Dose: Methylprednisolone 0.5-1.0 mg/kg/day until stable
	If improving: Transition to oral steroid at start of taper. Dose suggested: 60 mg prednisone daily x 2 weeks Taper over 4 weeks or more to reduce recurrence of symptoms. May consider re-initiation of immunotherapy
	If progressing: Treat as Grade 3-4 Hospitalize patient. Multidisciplinary evaluation of toxicity
Grade 3/4	Discontinue immunotherapy (*not in case of hypothyroidism*) Hospitalization indicated Increase dose of Methylprednisolone 2.0-4.0 mg/kg/day until stable
Refractory	If no improvement or progression, additional immunosuppressant treatment may be needed -Infliximab 5 mg/kg (except if contraindicated) -Mycophenolate mofetil 1 gram twice daily -Cyclosporine or intravenous immunoglobulin (IVIG)

Steroid Therapy Supportive Care

- When used, taper over at least 30 days
- Rapid taper may result in recurrence of toxicity
- Proton pump inhibitor
- Antimicrobial/antifungal prophylaxis
  - Sulfamethoxazole/trimethoprim
  - Voriconazole
- Vitamin D and calcium
  - Calcium carbonate-vitamin D3 600 mg (1,500 mg)-400 IU once daily

Patient Education

- Different AE profile than chemotherapy
- Early recognition of irAEs is essential to effective treatment
- Patients must notify their care provider if they develop symptoms or are admitted to local facility.
- irAEs are related to the mechanism of action of immunotherapies
- irAEs are treatable and respond well to steroids
- Time to response differs from standard therapy

Summary

- Toxicities can be life-threatening if not managed promptly
- Rapid diagnostic and treatment intervention is imperative for optimal control and prevention of “end-organ” damage
- Persistent grade 2 irAEs and grade 3 or 4 are treated with corticosteroids
- Use of standardized algorithms for monitoring and AE management is beneficial
- Early discontinuation of steroids may increase risk of relapse or progression of symptoms
- Taper of steroids should be under the direct supervision of the health care provider
- Re-initiation of treatment may be possible with optimal management
- Decision to restart treatment is not always clear