Checkpoint Inhibitor Treatment and Immune – Related Adverse Events

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Introduction / Basic Principles

- Cancer Cells
  - originate from tissue in the body
  - have damaged DNA
  - trick the immune system into using checkpoint pathways earlier than normal
  - grow out of control

- What are Checkpoint pathways?
  - part of the system of “checks and balances” that allow the immune cells to evaluate their attack
  - function as “ brakes” when response is no longer needed

- Checkpoint Inhibitors block these checkpoint pathways and tell the immune cells to resume the attack.

- T-cells are able to continue fighting the cancer but also have effect on normal body tissue.

Checkpoint Inhibitor Treatment and Immune – Related Adverse Events

- Blockade of CTLA-4 and PD-1 can lead to the development of Immune-related adverse events (irAEs)

- Common irAEs in patients treated with checkpoint inhibitor include :
  - Dermatitis
  - Enterocolitis
  - Endocrinopathies (Pituitary, Thyroid, Adrenal, Testes)

Checkpoint Inhibitor Treatment and Immune – Related Adverse Events

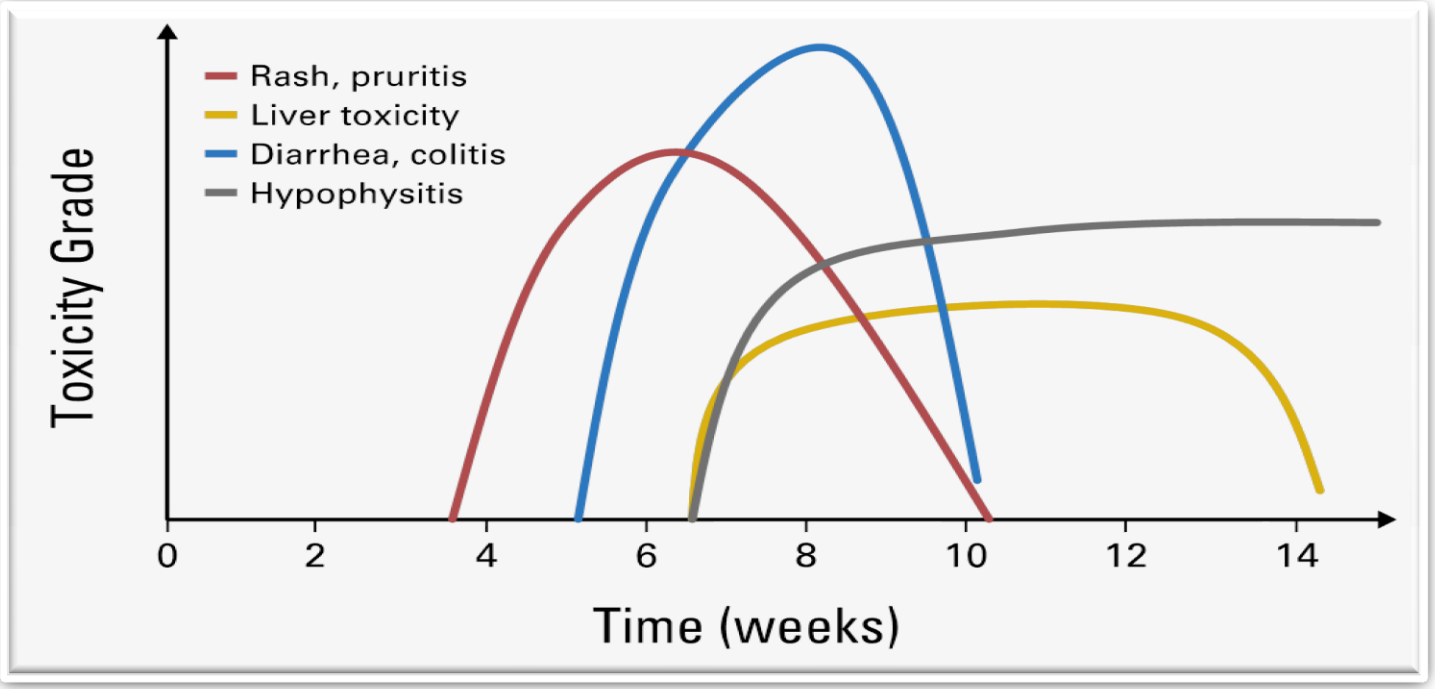
- irAE- any adverse event associated with drug exposure and consistent with an immune-mediated mechanism of action
- Infections and other etiologies should be ruled out or deemed unlikely as contributing to the irAE
- 4 main categories : GI, Liver, Endocrine, Skin
- At 3 mg/kg ipilimumab dose level in melanoma :
  - High Grade (grades 3/4) irAE rate is between 10-15 %
- At 10 mg/kg ipilimumab dose level in melanoma :
  - (adjuvant trials)
  - High Grade (grades 3/4) irAE is ~25%
- At 3mg/kg dose of PD-1 antibodies in melanoma
  - High Grade (grades 3/4) irAE is ~ 8-10%

Checkpoint Inhibitor Treatment and irAE's – Basic Issues

- Most irAEs occur during first 12 weeks of therapy; i.e. during induction
- Steroids can be used to manage almost all irAEs and will reverse almost all
- Prolonged steroid tapers are required (30-45 days)
- irAEs can wax and wane, particularly colitis and hepatitis
- Late irAE's can occur: one episode has been seen at month 47 during maintenance (Ipilimumab adjuvant trial)
- Each irAE has different kinetics of onset:
- Skin first, then colitis, then hypophysitis and finally hepatitis

Attia. J Clin Oncol. 2005;23:6043; Downey. Clin Cancer Res. 2007;13:6681; Lutzky. ASCO. 2009 (abstr 9034); van Elsas. J Exp Med. 1999;190:355; Weber. J Clin Oncol. 2008;26:5950.

Kinetics of Induction: irAEs with ipilimumab



Weber et al J Clin Oncol 2012

Dermatitis With Checkpoint Inhibition

- Most frequently with ipilimumab
- Advise patients to report skin related changes (rash & itching)
- Withhold ipilimumab in patients with moderate to severe signs and symptoms
  - Moderate- non-localized rash (diffuse,< or = 50% of skin surface)
  - Severe or Life Threatening-Stevens-Johnson syndrome, toxic epidermal necrolysis or rash complicated by full thickness dermal ulceration

- Permanently discontinue ipilimumab for :
  - Life threatening or immune-mediated dermatitis such as generalized exfoliative, full thickness dermal ulceration, ulcerative or bullous dermatitis, skin necrosis, SJS or TEN
  - Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day

Colitis and Enteritis With Checkpoint Inhibition

- Diarrhea is a common irAE (37% all grade and 12% grades 3/4) with ipilimumab, less so with PD-1 blockade
- Most cases respond to symptomatic treatment or high-dose steroids with a long taper (30 days)
- Infliximab is used in steroid-refractory cases
- Can rarely lead to GI perforation (1%), profound ileus or megacolon requiring surgery
- Colonoscopy or sigmoidoscopy shows diffusely erythematous, friable, and occasionally ulcerated mucosa

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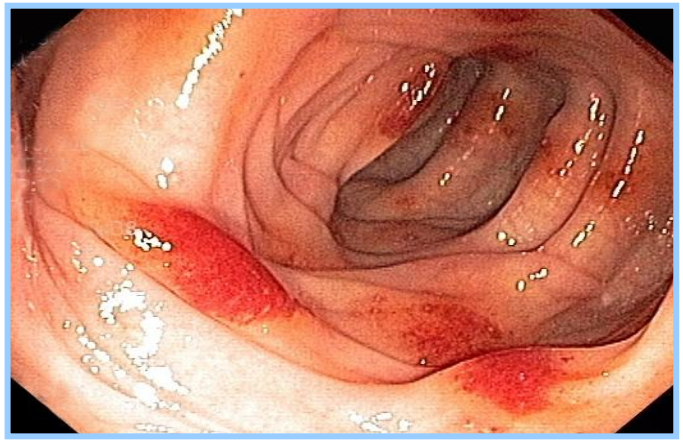
Colitis and Enteritis With Checkpoint Inhibition

- Colonoscopy
  - Multifocal circumscribed erythematous lesions
- Histopathology
  - Predominantly chronic inflammation



J Clin Oncol. 2006 May 20;24(15):2283-9.

Colitis and Enteritis With Checkpoint Inhibition

- Inflammation can occur anywhere in GI tract; mucositis, gastritis, enteritis, colitis

- Diarrhea : Requires Attention
  - New Watery
  - Increased frequency > 50% baseline
  - Duration
  - Bloody
  - (stress to patients to keep track of how many stools per day and to call for diarrhea!)

- Grade 1,2 (4-6 stools over baseline)
  - Withhold ipilimumab
  - Treat Symptomatically (Imodium first, add Lomotil if Imodium does not help in 24 hours)
  - Rule out other causes
  - No Steroids
  - Follow Closely for resolution

Colitis and Enteritis With Checkpoint Inhibition

- Grade 3,4 (> or = 7 stools over baseline)
  - Permanently discontinue ipilimumab
  - Duration and magnitude are important to determine need for hospitalization
  - Endoscopy is often useful, even for prolonged grade 2 diarrhea or any sign of bright red blood per rectum
  - Oral Budesonide and High Dose Steroids:
    - Budesonide 9 mg po daily x 10-14 days
    - 120 mg methylprednisolone IV daily
    - Prednisone taper, over 1 month
  - If persists (e.g. 72 hours) consider Infliximab 5 mg/kg

Endocrinopathies With Checkpoint Inhibition

- Relatively infrequent (6% all grades)

- Symptoms:
  - headache (can be severe), fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment [1-3]

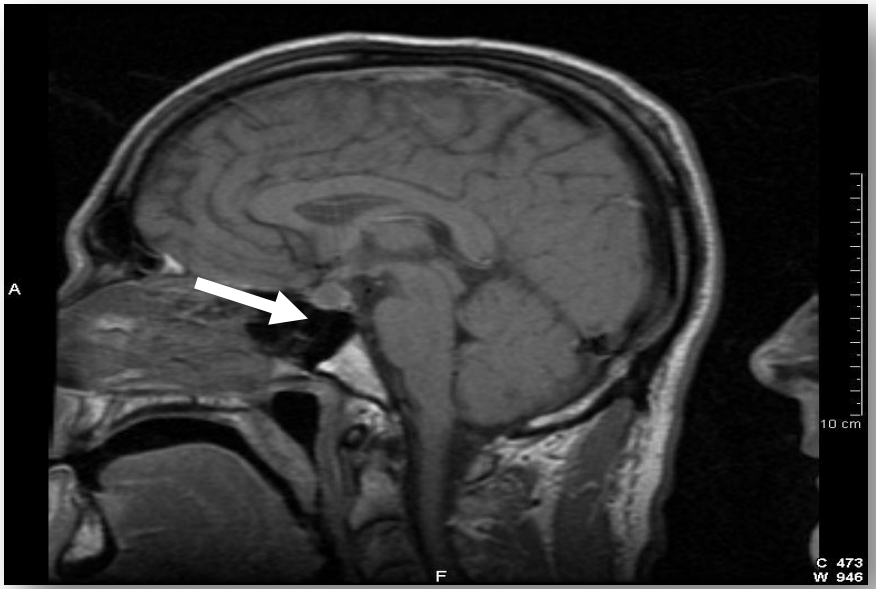
- Observed so far:
  - panhypopituitarism, hypothyroidism, hyperthyroidism
  - pancreatitis, adrenal insufficiency

- Management [1-3]
  - discontinue ipilimumab; work-up including labs and brain MRI, temporary corticosteroid administration with a brief taper over 10-20 days
  - replace deficient hormones
  - symptoms resolve with treatment [1-3]
  - slow return of some endocrine functions [1,2]

[1]Blansfield JA, et al. J Immunother 2005;28:593-598; [2]Attia P, et al. J Clin Oncol 2005;23:6043-6053; [3]Phan GQ, et al. Proc Natl Acad Sci USA 2003;100:8372-8377.

Hypophysitis With Checkpoint Inhibition

Hypophysitis With Checkpoint Inhibition



12/3/04- Headache/Fatigue
Pituitary size= 10.8 mm
Sagittal MRI section from patient 7 at the time of clinical symptom onset.

Blansfield JA, et al. J Immunother 2005;28:593-598

LFTs with Checkpoint Inhibition

- Liver function tests (LFT) must be assessed prior to administration of each dose of checkpoint inhibitor

- LFT elevations in patients may be associated with symptoms of hepatotoxicity (jaundice, right upper quadrant pain, vomiting) or may be completely asymptomatic; many patients have other non-specific symptoms (fever, malaise)

- All subjects must meet LFT criteria before each dose of checkpoint protein inhibitor
  - With no liver mets < 2.5X ULN for AST, ALT
  - Liver mets; < 5X ULN for AST, ALT, < 2.5X ULN for total bilirubin

LFTs with Checkpoint Inhibition

- Elevation LFTs > 3 fold baseline (>2.5 X ULN; grade 2) requires close attention
- Intensified monitoring; labs every 3 days
- Consider disease burden, medications, infections; imaging; consider biopsy
- LFTs >8x and/or T. Bili >5x
  - Intensified monitoring: Labs every 1-3 days
  - High dose steroids: methylprednisolone 120 mg IV daily
  - If after 3 days no improvement or rebound: Mycophenylate 1 g BID
  - If no improvement 5-7 days: 0.10 to 0.15 mg/kg/day tacrolimus (trough level 5-20 ng/ml)
  - If no improvement in 5-7 days: infliximab 5 mg/kg once

Other irAEs With Checkpoint Proteins

- Pancreatitis
  - Amylase/lipase elevation, abdominal pain low, and out of proportion to elevation of lab tests
- Uveitis
  - Redness, change in vision; ophtho evaluation
  - Topical corticosteroid eye drops
- Neuropathy (rare)
  - Mono- and Poly-neuropathies, ascending motor neuropathy
  - Rule-out cord compression and leptomeningeal disease
  - Consider steroids

PD-1 Antibody-Induced IrAEs

- Similar spectrum of adverse events, but rate of grades 3-4 irAEs about 5-6%
- Pneumonitis that is symptomatic is more common with PD-1 antibodies at 1-2%
- Grades 3-4 colitis are rare, at 1%
- Thyroiditis is more common, but hypophysitis is present at about the same rate at 1-2%
- Colitis, when present, has the same often prolonged course as with ipilimumab

Nivolumab-related Select AEs

-037 Phase III Trial of Nivolumab vs Chemotherapy

Select AE Organ Category Patients, n (%)	Nivolumab (N = 268)[A]	
	Any Grade	Grade 3–4
Skin	78 (29)	1 (<1)
Gastrointestinal	31 (12)	3 (1)
Endocrine	21 (8)	0 (0)
Hepatic	12 (5)	2 (1)
Pulmonary	6 (2)	0 (0)
Hypersensitivity/infusion reaction	5 (2)	1 (<1)
Renal	4 (2)	1 (<1)

- All grade 3-4 drug-related AEs belonging to the select AE categories resolved
- Corticosteroids were the most common immunosuppressive medication used
- In total, less than 5% of patients reported grade 3–4 select AE

- [A] Included all treated patients and events reported between the first dose and 30 days after the last dose of study therapy
- Weber JS, et al. Lancet Oncol. 2015;16:375-384.

Management of Pneumonitis With PD-1 ABS

- Relatively rare: 0.5 to 1.5% of patients at grades 2-3
- We routinely check pulse oximetry in all PD-1/PD-1/IPI patients
- Get a chest X-ray in anyone on PD-1 ab with SOB, chronic cough, increased sputum, and have a low threshold for obtaining a CT of the chest
- High dose steroids with at least 45-60 day tapers with starting doses of at least 1-2 mg/kg are required
- CT findings will lag behind the patient's symptoms
- Steroids may need to be re-tapered if symptoms return
- Use infliximab at 5 mg/kg if without relief in one week

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Clinic Visits

- First visit:
  - Check labs (LFT, Thyroid)
  - Educate on importance of detecting and reporting symptoms early
  - Discuss checklists and key points about irAE's
  - Provide medication guide and wallet card
  - Instruct patient on importance of seeking medical attention for irAE's
  - Instruct patient not to take any medications or supplements without discussing this with his/her HCP
- Follow up visits:
  - Before each infusion (and more frequently as needed) check lab values including AST, ALT, total bilirubin and thyroid function tests
  - Question patient about irAEs using checklists
  - Reinforce importance of early detection and prompt reporting
  - Instruct patient on appropriate procedure for reporting symptoms or seeking medical attention when the office is closed
  - Remind patient that symptoms may occur weeks to months after the infusion
  - Remind patient not to take and medications or supplements without discussing this with his/her HCP

Panel Discussion

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