Checkpoint Inhibitor Treatment and Immune – Related Adverse Events

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• I **do not intend** to discuss off-label uses of products during this activity.
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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

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

Colitis and Enteritis With Checkpoint Inhibition

► Colonoscopy
  • Multifocal circumscribed erythematous lesions

► Histopathology
  • Predominantly chronic inflammation

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 impairment¹-³

► Observed so far:
  • panhypopituitarism, hypothyroidism, hyperthyroidism
  • pancreatitis, adrenal insufficiency

► Management¹-³
  • 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 treatment¹-³
  • slow return of some endocrine functions¹,²

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.

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

- 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

- Included all treated patients and events reported between the first dose and 30 days after the last dose of study therapy


<table>
<thead>
<tr>
<th>Select AE Organ Category</th>
<th>Nivolumab (N = 268)&lt;sup&gt;A&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Any Grade</td>
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<tr>
<td>Skin</td>
<td>78 (29)</td>
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<tr>
<td>Gastrointestinal</td>
<td>31 (12)</td>
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<tr>
<td>Endocrine</td>
<td>21 (8)</td>
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<tr>
<td>Hepatic</td>
<td>12 (5)</td>
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<tr>
<td>Pulmonary</td>
<td>6 (2)</td>
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<tr>
<td>Hypersensitivity/infusion reaction</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Renal</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

<sup>A</sup> Included all treated patients and events reported between the first dose and 30 days after the last dose of study therapy
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