Management of IRAE

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and
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<table>
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<th>Consulting/Advisory Board</th>
<th>Contract Research</th>
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irAE Oversight Is an Important Part of Patient Management

• Immuno-oncology therapies associated with specific irAEs may reflect the relationship of those therapies to immune activation\(^1-3\)
  – Management of irAEs is influenced by type of AE, its severity, and individual patient profile\(^3,4\)

• Monitoring for irAEs involves a comprehensive review at each clinical visit\(^4\)

Tumor Immunology: Overview

Dendritic cell

TUMOR

Cytokines

Activated T cell

T-cell clonal expansion

Resting T cell

LYMPH NODE

Tumor antigen

1

Dendritic cell

2

3
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

CTLA-4 mAbs: Ipilimumab, Tremelimumab

PD-1 mAbs: Nivolumab, Pembrolizumab

PD-L1 mAbs: Atezolizumab, Avelumab, Durvalumab
The immune system is capable of recognizing and eliminating tumor cells in the tumor microenvironment. Innate and adaptive immunity act as a complementary network of self-defense against foreign threats.\(^1\)

Tumors can use various mechanisms to escape detection and enable growth.\(^2,3\)
• The precise pathophysiology underlying immune-related adverse events is unknown
• Immune checkpoints play in maintaining immunologic homeostasis
• PD-1 may be involved in maintaining self-tolerance
• Suppression of the high numbers of CTLA-4-expressing Tregs in the GIT, unleashing Th17-driven inflammatory responses
• Excessive expansion of Th17 cells in the GIT, associated with alterations in the gut microbiota and exacerbation of autoimmune disorders
PATHOPHYSIOLOGY

• Increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies

• Increase in the level of inflammatory cytokines including IL-17

• Enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland
Toxicity Management
If not vigilant, may result in more serious immune-related AEs
Early recognition and management important to decrease morbidity and mortality

- Proactive Monitoring
- Early recognition and reporting
- Prompt Appropriate Management
- Vigilant follow up
Kinetics of Onset and Resolution of CTLA4

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

Time (weeks)
Toxicity Grade

<table>
<thead>
<tr>
<th></th>
<th>Any grade, n (%)</th>
<th>Grade 3–4, n (%)</th>
<th>Grade 5, n (%)</th>
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<tbody>
<tr>
<td>Any irAEs</td>
<td>962 (64.2)</td>
<td>266 (17.8)</td>
<td>9 (0.6)</td>
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<td>Dermatologic</td>
<td>672 (44.9)</td>
<td>39 (2.6)</td>
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<td>GI</td>
<td>487 (32.5)</td>
<td>137 (9.1)</td>
<td>3 (0.2)</td>
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<td>Endocrine</td>
<td>68 (4.5)</td>
<td>34 (2.3)</td>
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<tr>
<td>Hepatic</td>
<td>24 (1.6)</td>
<td>16 (1.1)</td>
<td>2 (0.1)</td>
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<tr>
<td>Ocular</td>
<td>20 (1.3)</td>
<td>6 (0.4)</td>
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<tr>
<td>Neurologic</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>1 (&lt;0.1)</td>
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<tr>
<td>Cardiovascular (myocarditis)</td>
<td>2 (0.1)</td>
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GI: gastrointestinal; irAEs: immune-related adverse events.

*This pooled analysis includes patients received ipilimumab at various doses, ranging from 0.1 to 20 mg/kg.

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Kinetics of Onset and Resolution of PD-1/PD-L1 Treatment-Related Skin and GI AEs (≥ 10% of Pts)

<table>
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<th>Median Time (Wks)</th>
<th>Approximate Proportion of Patients (%)</th>
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<tr>
<td>1</td>
<td>5</td>
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<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
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</table>

*Any grade.

Kinetics of Onset and Resolution of Less Common PD-1/PD-L1 Treatment-Related AEs (< 10% of Pts)

<table>
<thead>
<tr>
<th>Median Time (Wks)</th>
<th>Approximate Proportion of Patients (%)</th>
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<tbody>
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</table>

- Endocrine*
- Hepatic*
- Pulmonary*
- Renal*

*Any grade.
General Guidelines for Management of Immune-Related AEs

- **Grade 1: asymptomatic to mild symptoms**
  - Observation
  - Intervention not needed

- **Grade 2: moderate symptoms**
  - Local or noninvasive intervention indicated
  - Withhold drug, consider re-dose if toxicity resolves to grade ≤ 1
  - Low-dose corticosteroids likely needed
  - May be able to continue treatment

- **Grade 3: medically significant but not immediately life-threatening**
  - Stop immunotherapy immediately
  - Hospitalization indicated
  - High-dose steroids indicated
  - Slow steroid taper over ≥ 1 mo once toxicity resolves to grade ≤ 1

- **Grade 4: life-threatening consequences**
  - Urgent intervention
  - Permanently discontinue treatment
### Table 2 | General management of ipilimumab immune-mediated adverse events*

<table>
<thead>
<tr>
<th>Severity of adverse event</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| Mild                     | **Continue ipilimumab**  
Increase frequency of monitoring  
Initiate supportive care | Frequent monitoring for resolution or escalation to moderate or severe (see below) |
| Moderate                 | **Withhold ipilimumab**  
Increase frequency of monitoring  
Initiate supportive care  
Institute appropriate medical evaluation and interventions, including relevant consultations, as indicated | Frequent monitoring for resolution or escalation to severe (see below)  
Resume ipilimumab once symptoms resolve or improve to mild |
| Severe or life-threatening | **Permanently discontinue ipilimumab**  
Increase frequency of monitoring  
Initiate supportive care  
Institute appropriate medical evaluation and interventions, including relevant consultations, as indicated  
Administer systemic steroids (1–2 mg/kg of prednisone or equivalent daily) | Frequent monitoring for resolution; if symptoms recur or worsen, increase steroid dose  
Continue steroids until resolution or improvement to mild and then taper over 1 month  
Consider infliximab (if gastrointestinal toxicity) or mycophenolate (if hepatotoxicity) in the absence of contraindications |

*Adapted from the FDA-approved risk evaluation and mitigation strategy for ipilimumab. *4*In patients with moderate to life-threatening endocrinopathies, ipilimumab can be resumed once symptoms are controlled, the patient is stable on hormone-related therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
Experience of Immune-related adverse events (iRAEs) associated with Nivolumab and Ipilimumab in a single centre

• Retrospective, single center, non-interventional analysis

• EAP for Nivo & Ipi in SA

• Toxicity and iRAEs: all relapsed metastatic NSCLC, melanoma, HD and RCC

• Informed consent & institutional ethics approval obtained from HRSC

• Mainly descriptive:
  - Data & endpoint variables summarised using descriptive statistics in addition to statistical modeling.
Data Collection

• Data from different points in time throughout a patient’s medical history were reviewed.

• Included: treatment history, demographic features, disease characteristics, initial & course of treatment at the time of enrollment in the SA-EAP

• Treatment-related information incl. history of concomitant drug use, details of nivo and ipi treatment (date of first doses, no. of infusions & reason for discontinuation or omission).

• Adverse events reported - routinely documented & graded using NCI CTCAE version 4.0
Results

• 45 patients (28 males, 16 females)
• Median age: 63 yrs
• Median PS: 1

• **Nivolumab Group**
  - *Metastatic melanoma*: 3 patients
  - *NSCLC*: 18 patients
  - *RCC*: 2 patients
  - *HD*: 2 patients

• **Nivolumab** 167 cycles (median: 4, range: 1 - 16)

• **Ipilimumab Group**
  - *Metastatic melanoma*: 19 patients

• Ipilimumab 76 cycles (median: 4, range 1 - 4)
## IRAEs

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<th>IPILIMUMAB</th>
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<td>Skin Rash</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Colitis</td>
<td>0</td>
<td>1*</td>
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<tr>
<td>Uveitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>0</td>
<td>3**</td>
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<tr>
<td>Hepatitis</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Autoimmune thrombocytopenia</td>
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<td>0</td>
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<tr>
<td>Nephritis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest Infections</td>
<td>3***</td>
<td>0</td>
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<tr>
<td>Vitiligo</td>
<td>0</td>
<td>2****</td>
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</tbody>
</table>

* Grade 3-4: required infliximab
** 1 hypophysitis / 2 hypothyroidism
*** Incl. TB infection in pt with NSCLC
**** Durable remission (5 & 7 yrs)
Documented IRAEs
Skin Rash

RCC
Nivolumab
Skin Rash

NSCLC
Combo: Ipi + Nivo
Dermatitis: Rash and Pruritus

- Low-grade rashes common
  - Reticular erythema
  - Papules to plaques

- Management
  - Photographic documentation and follow
  - Dermatology consultation and biopsy
  - Symptomatic treatment (eg, antihistamines)
  - Topical steroids
    - Oral steroids if more severe symptoms
  - Toxic epidermal necrosis is rare
  - Withhold for persistent grade 2 or grade 3
  - Permanently discontinue for grade 4

Ipilimumab-induced skin reactions and nephritis

The Price of Tumor Control: An Analysis of Rare Side Effects of Anti-CTLA-4 Therapy in Metastatic Melanoma from the Ipilimumab Network.
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0053745
Vitiligo

Metastatic Melanoma
Ibilimumab
7 yrs remission
Vitiligo

Forehead

Right hand

Metastatic Melanoma
Ipilimumab
Durable Remission- 7 yrs
Immune-Related Colitis
Immune-Related Colitis

Ulceration in Descending Colon

Focal Active Colitis

Alterations in Crypt Epithelium
Gastrointestinal irAEs

- Diarrhea is a common irAE
  - All grades: 27%
  - Grade 3/4: 5%
- Appearance on colonoscopy or sigmoidoscopy
  - Diffusely erythematous, friable, and occasionally ulcerated mucosa
- Colon biopsy
  - Usually inflammatory colitis with CD4>CD8 infiltrate in interstitium
- Most cases respond to symptomatic treatment or high-dose steroids with a long taper (over 1 month)
- Infliximab is used in steroid-refractory cases
- Can rarely lead to gastrointestinal perforation (1%), profound ileus, or megacolon requiring surgery

Gastrointestinal irAEs
Colitis

Metastatic Melanoma
Ipilimumab
Also hypophysitis
Durable Remission – 5 years
Hepatitis
Management of Hepatitis (Grade 2)

- Elevation LFTs > 2.5 x ULN; bilirubin > 1.5 x ULN (grade 2)
  - Requires close attention
  - Hold the dose
  - Intensified monitoring; labs every 2-3 days until grade 0/1 reached
  - Consider etiology
    - Disease burden
    - Medications
    - Viral hepatitis
    - Sepsis
  - Investigations as needed
    - Imaging
    - Consider biopsy
Management of Hepatitis (Grade ¾)

• If the LFTs > 5 x ULN or total bilirubin > 3 x ULN
  – Intensified daily monitoring
  – High-dose steroids: IV methylprednisolone 120 mg/day for 48 hrs
  – If no improvement after 3 days
    • Mycophenolate 1 g BID PO
  – If no improvement in 5-7 days
    • Tacrolimus 0.10 to 0.15 mg/kg/day (trough level 5-20 ng/mL)
  – If no improvement in 5-7 days
    • Infliximab 5 mg/kg once; can be given every 2-4 wks; can be a significant immune suppressant and is expensive
Pneumonitis
Pneumonitis

NSCLC
Nivolumab
Treatment discontinued
Post Steroid Therapy
Pneumonitis

NSCLC
Nivolumab
TB infection
TB infection

22 APRIL 2016
Disease Progression During Nivolumab Therapy
# Pneumonitis Management

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<tr>
<th>Grade of pneumonitis</th>
<th>Symptoms</th>
<th>Management</th>
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<td>Grade 1</td>
<td>None</td>
<td>Delay treatment</td>
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<td>Radiographic changes only</td>
<td>Repeat imaging every 3 weeks</td>
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<td>Grade 2</td>
<td>Mild to moderate</td>
<td>Delay treatment</td>
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<td>Dyspnea and cough</td>
<td>Consider admission to hospital</td>
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<td></td>
<td>Methylprednisolone IV 0.5–1.0 mg/kg/day</td>
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<td>Taper steroids over 1 month</td>
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<td></td>
<td>Repeat imaging in days to weeks</td>
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<tr>
<td>Grade 3–4</td>
<td>Severe</td>
<td>Delay treatment, consider permanent cessation</td>
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<td>Hypoxia</td>
<td>Admit to hospital or ICU</td>
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<td></td>
<td>Life-threatening respiratory compromise</td>
<td>Methylprednisolone IV 2–4 mg/kg/day</td>
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<td>Consider additional immunosuppression at 48 hours</td>
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<td>Taper steroids over 6 weeks</td>
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<td></td>
<td>Repeat imaging in days to weeks</td>
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Pituitary enlargement

6/30/04 - Baseline (4.5 mm)

12/3/04 - Headache/fatigue (10.8 mm)
Less Frequent irAEs

- Uveitis
- Neuropathies
- Guillain-Barré syndrome
- Myasthenia gravis
- Pulmonary
- Thrombocytopenia
- Pancytopenia
- Pancreatitis
- Sarcoid
General Principles

- GI IrAEs anti-CTLA-4 > anti-PD-1 inhibitors
- Pneumonitis > PD-1 inhibitors
- > Grade 3 or 4 adverse events with CTLA-4 blockers
- **Combination** = more toxicity
- **Dose** alters grade and frequency of irAEs
General Principles

- Early Recognition
- Immediate Action

Optimal Outcome
(decrease morbidity & mortality)
Conclusion

• Major advances in immunotherapy in cancer treatment
• Long term remissions
• Possible cures
• Different toxicity profiles
Thank You