ENDOCRINE ADVERSE EVENTS ASSOCIATED WITH CHECKPOINT IMMUNOTHERAPY

Lauren Clarine DO, Renil Rodriguez Martinez MD, Matthew Levine MD, Amy Chang MD, and Megan McGarvey MD
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Immune checkpoint inhibitors in the news this year

The New York Times

*Immune System, Unleashed by Cancer Therapies, Can Attack Organs*

*Harnessing the Immune System to Fight Cancer*

*Setting the Body’s ‘Serial Killers’ Loose on Cancer*

*Cell Wars: The Science of Immunotherapy*
Background

- In recent years, immune checkpoint inhibitors have emerged as effective therapies for advanced neoplasias.

- These aim to improve the ability to immunologically reject the tumor by generating an adequate immune response and breaking tumor-induced immune tolerance.

- Immune regulatory monoclonal antibodies developed have focused on inhibiting various checkpoints:
  - *Cytotoxic T lymphocyte antigen 4 receptor (CTLA-4)*
  - *Programmed death -1 (PD-1) receptor pathway*
Background

- **2011**: Ipilimumab (anti-CTLA4 Ab) approved for treatment of metastatic melanoma
- **2013**: Science Magazine named cancer immunotherapy “the breakthrough of the year”
- **2014-2015**: Nivolumab and pembrolizumab (anti-PD1) approved for melanoma, RCC, and NSCLC
  - Tremelimumab (anti-CTLA4 Ab) received FDA approval for malignant mesothelioma
- **2016**: Atezolizumab (anti-PD-L1 Ab) received FDA approval for treatment of metastatic NSCLC
- **2017**: Durvalumab (anti-PD-L1 Ab) and Pidilizumab (anti-PD-1 Ab) are in clinical trials
Background

- Immune checkpoint inhibitors have many indications thus far:
  - *Metastatic melanoma*
  - *Metastatic non-small cell lung cancer*
  - *Advanced renal cell carcinoma*
  - *Classical Hodgkin lymphoma that has relapsed or progressed after stem cell transplantation*
  - *Metastatic squamous cell carcinoma of the head and neck*
  - *Malignant mesothelioma*

- Anti-CTLA4 and anti-PD1 Ab have different mechanisms of action, but allow for increased T cell activation, proliferation, and activity
Background

- In contrast to conventional chemotherapy, boosting the immune system leads to a unique constellation of inflammatory toxicities known as immune-related adverse events (irAEs).

- Recognition and management of irAEs is crucial to be able to use these agents. 
  - *While most irAEs are mild, some can be life-threatening*

- Use of these agents is set to increase due to their dramatic impact on survival in a variety of advanced staged cancers.
Methods

- A retrospective chart review was done of patients who received immune checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab) at Scripps over 2 years (Jan 2015 – Dec 2016)

- Demographic data, number of infusions, and data involving the development and progression of endocrine disorders were collected

- Assessment of hypophysitis, thyroid dysfunction, adrenal insufficiency, and type 1 diabetes was done

- Endocrine disorder severity was graded from 1 – 4 based on the NIH Common Terminology Criteria for Adverse Events, with 1 being asymptomatic and 4 being life-threatening requiring urgent intervention
Results

117 patients

77 men (66%)
40 women (34%)

26 received Anti-CTLA4 Ab
83 received Anti-PD1 Ab
8 received Anti-CTLA4 Ab + Anti-PD1 Ab

Anti-CTLA4 Ab = ipilimumab
Anti-PD1 Ab = nivolumab and pembrolizumab
Results

- Anti-CTLA4 Ab = ipilimumab
- Anti-PD1 Ab = nivolumab and pembrolizumab
- * = nivolumab patients
- AI = adrenal insufficiency
- T1DM = type 1 diabetes

N = 117

77 men (66%)
40 women (34%)

N = 26
Anti-CTLA4 Ab

N = 7 (27%)
Hypophysitis

N = 6 → AI
N = 2 → hypothyroid

N = 4 (16%)
Hypothyroid

N = 1
Thyroiditis

N = 83
Anti-PD1 Ab

N = 21 (25%)
Hypothyroid

N = 2 (4%*)
T1DM

N = 1
Hypophysitis

N = 1
Thyroiditis

N = 8
Anti-CTLA4 Ab +
Anti-PD1 Ab

N = 1
Hypophysitis

N = 1 → AI
and hypothyroid

77 men (66%)
40 women (34%)
Discussion

Our study found that the development of an endocrine disorder is very common with the use of immune checkpoint inhibitors

- 37 patients (32%) who received immune checkpoint inhibitor infusions developed some type of endocrine adverse event (irAE)

- Gender was not a risk factor for development of an endocrine irAE
  - 32% of women and 27% of men developed an endocrine irAE
Discussion

- The most common endocrine irAEs were:
  - Hypophysitis
  - Primary hypothyroidism

- Early diagnosis and treatment of the endocrinopathy is important as it may prevent discontinuation of cancer treatment
  - Patients who developed hypophysitis and T1DM had higher grade irAEs (grade 3), were hospitalized, and immunotherapy was eventually discontinued
Discussion

- There is a lack of standardized screening protocols for the development of immune related endocrine adverse events
  - Variability in obtaining baseline and subsequent thyroid function tests (TFTs)
  - Variability in pituitary hormone testing
Discussion

It is important to monitor closely for development of irAEs throughout therapy given variable onset

- Most irAEs occurred between the 2nd and 5th infusion
- Six irAEs occurred after the 1st infusion
- One irAE occurred after 14 infusions
- Reviews (2016) indicate a median onset of 7 – 20 weeks, but current protocols recommend discontinuing screening at week 16\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Endocrine Disorder</th>
<th>Average number of doses given before development of irAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophysis</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5.5</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>2</td>
</tr>
<tr>
<td>T1 diabetes</td>
<td>2</td>
</tr>
</tbody>
</table>
Discussion - Hypophysitis

- Hypophysitis was the most common irAE associated with anti-CTLA4 Ab therapy
  - 23% of those who received ipilimumab developed hypophysitis in our study
  - Incidence slightly higher than previously reported (0-17%)\(^3\)
  - Lower incidence reported for anti-PD1 Ab therapy (0.9 -1.2%)\(^1,4\)

- ACTH and TSH are the most common hormone deficiencies reported
  - Our study: 88% of those with hypophysitis had central adrenal insufficiency
  - Our study: 38% of those with hypophysitis had central hypothyroidism
Discussion - Hypophysitis

Incidence was not associated with a higher dose of ipilimumab in our study.

- Limitations: 2 doses unknown and small cohort

<table>
<thead>
<tr>
<th>Ipilimumab Dose (mg/kg)</th>
<th># of Patients Receiving Ipilimumab</th>
<th># of Patients Who Developed Hypophysitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>8</td>
</tr>
</tbody>
</table>
Discussion - Hypophysitis

While other hormone axes may recover, development of central adrenal insufficiency is likely to be permanent\textsuperscript{4}

- All 7 cases of central adrenal insufficiency did not have recovery of function in our study
  - Mean follow up period: 9 months

- 3 of 3 cases of central hypothyroidism have not resolved completely, although in 1 case, the dose requirement has decreased significantly
  - Recovery has been reported in 37 – 50\%\textsuperscript{5}
Discussion - Hypophysitis

High dose glucocorticoid therapy is currently recommended as standard treatment for hypophysitis and central adrenal insufficiency (AI)

- Albarel and colleagues did not show that high dose glucocorticoid therapy versus physiologic dosing improved the outcome\(^6\)
- In our study, 7 of 7 patients with central AI received supraphysiologic glucocorticoid therapy and the axis did not recover
- Consider using physiologic glucocorticoid replacement dosing for treatment of AI to avoid adverse effects
Discussion – Primary Thyroid Disorders

- Thyroid disorders were the most common endocrine irAE with anti-PD1 Abs
  - *Our study: incidence of any thyroid disorder was 24% with anti-PD1 therapy*
  - *Reported incidence is 0 – 19% for anti-PD1 therapy, 0 – 7% for anti-CTLA4 therapy, and 18 – 24% for combination therapy*¹⁴

- Specifically, hypothyroidism was most commonly seen

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>32%</td>
</tr>
<tr>
<td>pembrolizumab</td>
<td>9%</td>
</tr>
<tr>
<td>Anti-PD1 Ab</td>
<td>23%</td>
</tr>
</tbody>
</table>

- Cases of thyrotoxicosis developed into thyroiditis or hypothyroidism
Discussion – Primary Thyroid Disorders

- Routine thyroid autoantibody testing was not done in our study, however, may predict those that will develop permanent dysfunction versus transient drug induced thyroiditis
  - Weber and colleagues reported in a nivolumab series:
    - 26% of patients who developed thyroid dysfunction had thyroid autoantibodies at baseline
    - 36% developed autoantibodies during immunotherapy\(^7\)
  - Consider TPO Ab testing if abnormal thyroid function tests develop

- In our study, thyroid disease severity was grade 2 or less
  - None of our patients had discontinuation of therapy due to thyroid disorder development
Discussion - Type 1 Diabetes

- New onset T1DM has been linked to checkpoint immunotherapy

- Rapid progression to insulin dependence in those with pre-existing diabetes has also been reported\(^8\)

- The reported rate is 1% with each immune checkpoint inhibitor\(^9\)

- In our study, there was a higher percentage (4%) of patients receiving nivolumab who developed T1DM
  - New onset T1DM in one case
  - Rapid progression of diet controlled T2DM to insulin requiring in the second case
Conclusion

- Endocrine immune related adverse events are common with the use of checkpoint immunotherapy

- While most endocrine irAE are mild, they can be life-threatening; rapid identification and treatment can prevent discontinuation of cancer treatment and improve outcomes

- Hypophysitis was the most common endocrine irAE associated with anti-CTLA4 Ab therapy

- Primary thyroid disorders (hypothyroidism) were the most common endocrine irAE associated with anti-PD1 Ab therapy
Conclusion - Suggested Algorithm

Joshi et al. Clinical Endocrinology (2016) 85, 331–339

**Screen TFTs q month**

**Cont after wk 16**

*Clinical features* include: fatigue, tiredness, nausea, HEADACHE, visual disturbance, dizziness, diarrhoea, tachycardia, tremors, hypotension, hypoglycaemia, hyponatremia.

Baseline biochemistry prior to commencing immune checkpoint inhibitors (TSH, fT4, Cortisol, IGF 1, oestradiol/testosterone, LH, FSH, prolactin)

Check for clinical features* prior to each cycle

Screening bloods at 8 weeks (prior to cycle 3) and at 16 weeks, similar to baseline

If no clinical features and no biochemical abnormality. No further routine testing.

Consider possible endocrine dysfunction if later symptoms occur

*Screen TFTs q month*

*Cont after wk 16*

*Consider physiologic steroid dosing for AI*

*Consider BB before starting ATD given frequency of thyroiditis*
References


