Checkpoint inhibitors and autoimmune endocrinopathies

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Disclosures

• I have a patent application for a method to measure beta cell death in vivo

• I have consulted for Pfizer, BMS, Merck, Roche, Lilly, and Tiziana concerning treatment for Type 1 diabetes.

• I have no disclosures related to the material in this presentation
Immunotherapies targeting checkpoint inhibitors

The anti-tumor mechanisms of action of CPIs involve relief of negative T cell costimulatory signals, resulting from T cell “exhaustion”, that render T cells unable to kill tumor cells. This same mechanism of action would be expected to lead to immune related adverse events. Endocrine organs: pituitary, thyroid, adrenal, and β cells are prime targets for (auto)immune responses.
Cancer immunotherapy — immune checkpoint blockade and associated endocrinopathies

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Table 1 | Endocrine IRAEs in patients treated with ipilimumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Hypophysis</th>
<th>2(^{\circ}) or other adrenal insufficiencies</th>
<th>2(^{\circ}) or other hypothyroidisms</th>
<th>1(^{\circ}) hypothyroidism</th>
<th>Thyroiditis</th>
<th>1(^{\circ}) adrenal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2,938</td>
<td>184/2,017</td>
<td>37/608(^{11}) (6.1%)</td>
<td>42/555(^{12}) (7.6%)</td>
<td>23/410 (5.6%)</td>
<td>9/283 (3.2%)</td>
<td>2/256 (0.8%)</td>
</tr>
</tbody>
</table>

Table 3 | Endocrine IRAEs with PD1 and PDL1 antibodies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Hypophysis</th>
<th>Hyperthyroidism</th>
<th>Adrenal insufficiency</th>
<th>Hypophysitis</th>
<th>Other thyroid(^+)</th>
<th>T1DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2,702</td>
<td>160/2,573</td>
<td>71/2,153 (3.3%)</td>
<td>2/117 (1.7%)</td>
<td>10/1,658</td>
<td>3/224 (1.3%)</td>
<td>3/766</td>
</tr>
</tbody>
</table>

Totals with ipilimumab: 32.4%

Totals with PD-1 and PD-L1: 13.2%

Overall rates from Barroso-Sousa et al (2017):

- Hypothyroidism: 6.6% (3.8-13.2%)
- Hyperthyroidism: 2.9% (0.6-8.0%)
- Hypophysitis: 0.5% (0.4-6.4%)
- 1\(^{\circ}\) Adrenal insuff and IDD: 0.7% and 0.2%

*There have been > 15 case reports of CPI induced diabetes
The incidence of endocrine dysfunction was higher with combo vs ipi alone. The incidence of thyroid dysfunction and hypophysitis was highest with PD-1 inhibitors and ipi respectively.
Potential mechanisms of immune related adverse events

• Activation of effector T cells: Are these cells affected by checkpoint inhibitor? Are they present before treatment?

• Disturbance of normal mechanisms of tolerance? Are changes restricted to T cells?

• Tissue responses?
Features of diabetes induced with checkpoint inhibitors

- New onset of diabetes in elderly or dramatic increase in insulin requirements in a patient with known Type 2 diabetes.
- Time to dx: mean 10 mos w/o hx of DM but 3.5 mos with a hx of DM
- 7/17 present with diabetic ketoacidosis. Avg A1c=8.09%
- BMI=28.
- Both T1D associated (HLA-DR3,4) and protective alleles identified.
- May or may not have autoantibodies
- Triggers: incr px enzymes in 6/10, imaging c/w pxitis 2/6, infection 1/17; steroids in 4/17
- 4/17 with thyroid dysfunction, 1/17 with hypophysitis
- No FH of autoimmune diabetes but frequently a family history of autoimmune diseases
- Rapidly progresses to undetectable levels of C-peptide
- It does not appear that steroids will prevent complete loss of beta cell function
- Recovery is very uncommon
- Glucose lability is consistent with absolute deficiency of insulin.
Detecting Islet Ag-Specific T Cells in CyTOF

Direct heavy metal-conjugation on mutated streptavidin having cysteine residues (Newell EW et al., Nature Biotech 2013)

⇒ higher specificity with barcoding technology (and smaller sample size)
Tissue/drug interactions?
CTLA-4 staining was found on 2±1% of PRL-secreting cells and 3±2% of the TSH-secreting cells. It was not seen on GH, ACTH, FSH, or S100+ cells.
Why is autoimmune diabetes only seen with anti-PD-1/PD-L1 antibodies while thyroiditis is seen with PD-1 and CTLA-4 checkpoint inhibitors?
The new subpopulation has reduced expression of diabetes antigens and increased expression of immune inhibitory ligands.

(Rui et al, Cell Metabolism, 2017)
Conclusions

• Autoimmune endocrine adverse events are common after checkpoint inhibitor therapies. They can result in considerable morbidity.

• The reasons why some but not others develop these adverse events require further studies:
  • There appears to be selection of target organs based on the checkpoint inhibitor – hypophysitis is more common with anti-CTLA-4 mAb, thyroid abnormalities are more common with anti-PD-1/L1 antibodies, and diabetes is exclusively with anti-PD-1/L1 antibodies.
  • Endocrine events are more common with combinations.
  • Changes in T, B cells and Tregs may be found but the relationship between these findings and risk or development of the adverse events will require further studies.
  • Tissue specific changes and associated inflammation may be important determinants of proclivity to immune attack.

• Understanding the pathogenesis of checkpoint inhibitor associated adverse events may shed light on normal immune tolerance and suggest ways to prevent autoimmunity in this setting or spontaneous disease.
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