Immune Related Adverse Events (irAE) from Checkpoint Inhibitor Immunotherapy

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Disclosures

Advisory Board: Array BioPharma, Aduro, BMS, Incyte, Merck, NewLink Genetics, Novartis

Honoraria: BMS and Merck

Institutional Support: RGenix, Infinity, BMS, Merck, Array BioPharma, Novartis
Cancer historically understood as disorder of dividing cells
Cancer historically understood as disorder of dividing cells
Oncologists stop dividing cells
What happened in 1891?
Immunotherapy = Immune cell kills a cancer cell
Ways to enhance T cell attack

Mellman et al. Nature 2011
Ways to enhance T cell attack

Turning up The Activating

Mellman et al. Nature 2011
Ways to enhance T cell attack

Turning up The Activating

Blocking the Inhibiting

FDA Approved Targets

Turning up The Activating

Blocking the Inhibiting

Mellman et al. Nature 2011
Oncologists turn up immune system
What kind of side effects happen?
All organs can be involved

Postow, Sidlow, Hellmann *N Eng J Med* 2018
When do side effects happen?
Most nivolumab side effects happen in first 3 months (Any Grade; N = 474)

Circles indicate median and bars indicate ranges

Why do side effects happen?
Increasing T-cell activity against antigens that are present in tumors and healthy tissue

Increasing levels of preexisting autoantibodies

Tumor with antigen and activated T cells

Antithyroid antibodies

Increasing level of inflammatory cytokines

Enhancing complement-mediated inflammation due to direct binding of an anti–CTLA-4 antibody with CTLA-4 expressed on normal tissue

Activated T cell

Cytokines

Postow, Sidlow, Hellmann *N Eng J Med* 2018
T cells infiltrating myocardium

Norwood et al. JITC 2017
Thyroid dysfunction associated with antibodies (i.e. anti-thyroglobulin)

Osorio et al. Annals of Oncol 2017
Hematopoietic cell infiltration of the pituitary gland in mice injected with a CTLA-4 blocking antibody

Shintaro Iwama et al., Sci Transl Med 2014;6:230ra45
Peripheral cytokines associated with adverse events

Lim et al. Clin Cancer Res 2019
What do I do if I have a problem?
Important Publications

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

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side effects of immunotherapy

In an all-new episode of UpToDate Radio, members of our clinical faculty discuss the following important updates:

- Treatment for acute otitis media in young children (Dr. Sheldon Kaplow)
- Tenouron alferassine for the treatment of chronic hepatitis B virus infection (Dr. Anne Liu)
Does immunosuppression hurt immunotherapy benefit?
Steroids (to treat side effects) do not seem to affect ipilimumab efficacy

Infliximab does not seem to affect efficacy of ipilimumab

Retrospective study of 113 patients
32 patients with diarrhea (19 patients Grade ≥ 2 diarrhea)

29 patients received steroids
7 patients had infliximab

Arriola et al. *Clin Cancer Res* 2015
BUT high dose steroids (>7.5mg daily) for ipilimumab hypophysitis was associated with worse outcomes (n=98)
Future Questions

• Can mechanism based immunosuppression mitigate toxicity from steroids?

• What can toxicities teach us about autoimmune diseases?

• Long-term complications?
Thank you!
Back-up slides in case of questions
What about safety in patients with autoimmune conditions?
Safety in patients with underlying autoimmunity

1. Knowledge is limited since patients with autoimmunity not included in clinical trials

2. Retrospective studies suggest it may be safe

3. Risk/benefit discussion with patients

Kyi and Postow *JITC* 2014
Johnson et al. *JAMA Oncol* 2016
Menzies et al. *Annals of Onc* 2017
When is it safe to restart immunotherapy after toxicity?
38 patients with NSCLC who discontinued PD1/PDL1 due to toxicity and retreated with PD-1

- 26% recurrence rate of same irAE that caused discontinuation
- 84% improved to grade 1 or resolved but some recurrent toxicities were severe with 2 treatment related deaths
- No clear association between intensity of prior toxicity and likelihood of recurrent toxicity
- No clear benefit to resuming PD-1 in patients who responded prior to initial toxicity

Santini et al. Cancer Immunol Res 2018
Immunosuppression does not seem to affect nivolumab efficacy

<table>
<thead>
<tr>
<th></th>
<th>NIVO monotherapy with immunosuppression to treat a side effect N = 139</th>
<th>NIVO monotherapy without immunosuppression to treat a side effect N = 437</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%), [95% CI]</td>
<td>40 (28.8) [21.4–37.1]</td>
<td>141 (32.3) [27.9–36.9]</td>
</tr>
<tr>
<td>Median duration of response, mo (95% CI)</td>
<td>NR (9.3–NR)</td>
<td>22.0 (22.0–NR)</td>
</tr>
<tr>
<td>Median time to response, mo (range)</td>
<td>2.1 (1.2–8.8)</td>
<td>2.1 (1.4–9.2)</td>
</tr>
</tbody>
</table>

Most nivolumab + ipilimumab side effects happen in first 3 months (Any Grade; N = 448)

Sznol et al. *Journal of Clin Oncol* 2017
80 patients who discontinued CTLA4+PD1 due to toxicity of whom 77 (96% required steroids) [1]

- 18% recurrence rate of same irAE that caused discontinuation
- Some recurrent toxicities were severe
- No clear association between recurrent toxicity and prior steroid duration or use of additional immunosuppression
- Some association with lower recurrent toxicity risk with being off steroids and time since prior toxicity

Pneumonitis

Two doses of ipilimumab and four of nivolumab
Most side effects resolve

<table>
<thead>
<tr>
<th>AE</th>
<th>Median (95% CI)</th>
<th>% Resolved</th>
<th>Overall</th>
<th>Treated with IMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>3.9 (2.1 to 8.1)</td>
<td>27 of 33 (81.8)</td>
<td>23 of 29 (79.3)</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>3.6 (2.0 to 4.3)</td>
<td>69 of 73 (94.5)</td>
<td>62 of 65 (95.4)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>4.3 (3.1 to 5.6)</td>
<td>74 of 76 (97.4)</td>
<td>52 of 52 (100)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>15.1 (4.6 to NA)</td>
<td>13 of 21 (61.9)</td>
<td>9 of 16 (56.3)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4.5 (0.3 to 10.1)</td>
<td>6 of 6 (100)</td>
<td>5 of 5 (100)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1.9 (0.4 to 3.6)</td>
<td>7 of 7 (100)</td>
<td>4 of 4 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Sznol et al.  
Journal of Clin Oncol 2017
Outcomes look similar in patients who discontinue due to toxicity vs. those who continue treatment longer.
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