Immune-Related Adverse Events (IRAEs) due to Cancer Immunotherapy

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Cancer Immunotherapy 2016
Immune Checkpoints Regulate Different Components in the Evolution of an Immune Response

**CTLA-4 blockade:**
Ipilimumab

**PD-1 blockade:**
Nivolumab, Pembrolizumab

**PD-L1 blockade:**
Atezolizumab

Modified figure from: Cappelli LC, Shah AA, Bingham CO. Immune related adverse effects of cancer immunotherapy- Implications for rheumatology. Rheum Dis Clin. 2016,
# Approved Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecular Target</th>
<th>Malignancy Approved for</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab (Keytruda)$^1$</td>
<td>PD-1</td>
<td>Non-small cell lung cancer&lt;br&gt;Melanoma</td>
<td>2015&lt;br&gt;2014</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)$^2$</td>
<td>PD-1</td>
<td>Hodgkin lymphoma&lt;br&gt;Renal cell carcinoma&lt;br&gt;Non-small cell lung cancer&lt;br&gt;Melanoma&lt;br&gt;Head and neck</td>
<td>2016&lt;br&gt;2015&lt;br&gt;2014&lt;br&gt;2013&lt;br&gt;2016</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)$^3$</td>
<td>PDL-1</td>
<td>Urothelial carcinoma&lt;br&gt;Non-small cell lung cancer</td>
<td>2016</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)$^4$</td>
<td>CTLA-4</td>
<td>Melanoma, in combination with nivolumab&lt;br&gt;Melanoma</td>
<td>2014&lt;br&gt;2011</td>
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Improved Survival with Ipilimumab (Anti-CTLA4) in Patients with Metastatic Melanoma

PDLOMAS Activity in 2015

PD-1/PD-L1 Blockade

- Mel
- RCC
- NSCLC
- Bladder
- HNSCC
- Gastric
- Hodgkin
- B-Cell NHL
- CRC
- MSI High
- TNBC
- Ovarian
- Mesoth
- HCC
- Oesophag
- SCLC

Fig. 3. The clinical spectrum of IRAEs. IRAEs: immune-related adverse events.

irAEs from Cancer Immunotherapy with Checkpoint Inhibitors

CNS = central nervous system; GI = gastrointestinal; PG = pyoderma gangrenosum; PMR = polymyalgia rheumatica.
Clinical Characteristics of iRAEs – How to Distinguish from Cancer or Infection Symptoms?

<table>
<thead>
<tr>
<th>IRAE</th>
<th>Clinical Characteristics</th>
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<tbody>
<tr>
<td>Colitis</td>
<td>Diarrhea, perforation, death</td>
</tr>
<tr>
<td>Rash</td>
<td>Vitiligo, neutrophilic dermatoses, SJS</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Hypo/hyper</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Dyspnea, cough, respiratory failure</td>
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<tr>
<td>Hypophysitis</td>
<td>All hormonal axes or can be selective</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Can lead to heart failure, death</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Transaminitis, with or without elevated bilirubin</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Encephalopathy, aseptic meningitis, transverse myelitis</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Peripheral neuropathy, Guillain-Barré syndrome</td>
</tr>
</tbody>
</table>
General Features of Checkpoint Therapy IRAEs

- irAEs occur in up to 90% of patients with CTLA4 and 70% of PDI-treated patients
- Data on irAEs are not uniformly collected, and grading systems are suboptimal
- irAEs may predict favorable response to certain tumors
- Autoantibodies are generally absent

Timeline with AE Checkpoint Inhibitors

Dermatologic ++++
Gastroenterologic ++++
Endocrine +++
Neuro/Eye +
Rheumatic +
Renal +

irAEs with Checkpoint Inhibitor Therapy

• General
  – More common with anti-CTLA4 vs anti-PD1
  – Greater at high doses compared with low doses
  – More common with combination therapy
  – Immunosuppressive therapy is often required
  – Can exacerbate underlying AID?

• Single-center experience with ipilimumab (LD)
  – Of 298 patients treated with anti-CTLA4, 254 (85%) developed irAEs and 104 (35%) required therapy
  – Corticosteroids were needed in 103 patients (35%)
  – TNFi was needed in 29 patients (10%)

• Combo (CTLA4-Ig and anti-PD1)
  – irAE 55% - 27% - 15%

TNFi = TNF inhibitor.
Rheumatic Complications

- Rheumatic complications are among the most poorly defined irAEs, with a prevalence of 5%? Underdiagnosis?
- Severity grading non-standardized
- Arthralgia, arthritis, PMR, GCA, myalgia/myositis, sicca, SLE
- May be transient to chronic
- Often require high-dose glucocorticoids (0.5 to 1.0 mg/kg/day)
- Immunomodulatory therapy being explored on a case by case basis: oral DMARDs, TNFi, ?abatacept, ?other
  - Concern re. blunting or reversal of cancer treatment?
"We retrospectively characterized the clinical outcomes of 30 patients with preexisting autoimmune disorders who received ipilimumab and observed that 15 patients (50%) experienced irAEs or flares of their underlying autoimmune disorder, which were generally manageable with standard treatment."

EXTENDED REPORT

Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab

Laura C Cappelli, Anna Kristina Gutierrez, Alan N Baer, Jemima Albayda, Rebecca L Manno, Uzma Haque, Evan J Lipson, Karen B Bleich, Ami A Shah, Jarushka Naidoo, Julie R Brahmer, Dung Le, Clifton O Bingham III

CHECKPOINT IMMUNOTHERAPY: GOOD FOR CANCER THERAPY, BAD FOR RHEUMATIC DISEASES

Leonard Calabrese, Vamsidhar Velcheti

The most common toxicities seen with these agents include cutaneous reactions ranging from maculopapular rash to life-threatening disorders such as Sweet's syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis, among others. Gastrointestinal toxicity is common, especially diarrhoea, but a frank colitis may occur which can be life-
Hopkins Case Example

- 35 year old man with stage IV melanoma
- One dose of ipilimumab/nivolomab
- Develops colitis, responds to prednisone, tapered off after 1 month
- One subsequent dose of nivolumab monotherapy
- Develops severe conjunctivitis and sterile urethritis

Case courtesy of Laura Cappelli
Hopkins Case Example

• Within weeks, develops joint pain and swelling
• Initial synovitis in ankles and knee effusions, then wrists
• Synovial fluid: 11950 WBCs (92% PMN)
• Prednisone 120 mg daily, tapered to 40 mg daily over two weeks.
• Some improvement in swelling and stiffness, but persistent Sx
• Adalimumab -> one dose, marked improvement. But then....

Case courtesy of Laura Cappelli
Hopkins Case Example

- Sinus congestion and periorbital swelling, Adalimumab held
- 2 courses of antibiotics w/out improvement
- Sinus CT shows pan-sinusitis
- New Atrial fibrillation requiring cardioversion x 2
- Arthritis recurrent in spite of 40 mg prednisone
- No evidence for recurrence of melanoma
- Restarted Adalimumab with prompt resolution of all symptoms (joint, sinus, and cardiac)

Case courtesy of Laura Cappelli
Characteristics of Rheumatologic Complications – Hopkins Experience

• Patients tend to be seronegative for RF and CCP
• Additive course: starting in larger joints, often lower extremity, before involving hands
• True reactive arthritis has been seen
• Lack of response (in some) to 20 mg/d prednisone or much higher
Characteristics of Rheumatologic Complications – Hopkins Experience

- Erosive disease can occur
- Proliferative synovitis seen on ultrasound
- Often multiple IRAEs present
- Can persist after ICI discontinuation (we have seen up to 2 years)
- Subgroup of patients with milder disease being seen more recently (referrals changing)
Hopkins Case Example
Unresolved Questions

- How best to treat
- Step down or step up approach
- Long term effects of immunosuppression on tumor response
- Relationship between IRAE and tumor response
- Monitoring, treating those with pre-existing autoimmune disease on ICIs
- ....and many more!
Evolving Paradigms of Care for IRAEs

- Multidisciplinary team care
  - Identification of clinicians interested in learning about and caring for IRAEs: Heme-onc, GI, pulmonary, rheumatology, endocrine, dermatology, etc.
  - Case conferences, journal clubs
  - Studies of care of patients with established autoimmune disease
  - Clinical registries
  - Partnership with pharma