Immunotherapy in Melanoma: Use in Patients with Autoimmune Diseases

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Objectives

• Review the current place in practice for immunotherapy in melanoma
• Discuss the use of immunotherapy in patients with autoimmune conditions
Systemic Melanoma Treatment

• Adjuvant therapy
  – Interferon $\alpha$-2b or peginterferon $\alpha$-2b
  – Ipilimumab 10 mg/kg every 3 weeks x 4 followed by every 12 weeks for up to 3 years
  – Select patients: Talimogene laherparepvec (T-VEC)

• Metastatic disease
  – Immunotherapy – Aldesleukin (IL-2), ipilimumab, pembrolizumab, nivolumab
  – BRAF-pathway targeted therapy – vemurafenib, cobimetinib, dabrafenib, trametinib,
  – Chemotherapy – Dacarbazine, temozolomide, paclitaxel, combination therapy
Talimogene Laherparepvec (T-VEC)

- Herpes simplex virus (HSV) type-1 derived oncolytic virus
  - Selectively replicates in tumor cells → Cell lysis

- Phase III trial with 436 melanoma patients with stage IIIB to IV injectable melanoma sites not amenable to surgical resection
  - Response seen in both injected and uninjected lesions
  - Greatest benefit in stage IIIB/IIIC

<table>
<thead>
<tr>
<th></th>
<th>T-VEC</th>
<th>GM-CSF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response Rate</td>
<td>16.3%</td>
<td>2.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>26.4%</td>
<td>5.7%</td>
<td>Not available</td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>10.8%</td>
<td>&lt;1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall survival</td>
<td>23.3 months</td>
<td>18.9 months</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Systemic Therapy Options for Metastatic Melanoma

**First-line Therapy**
- Nivolumab (category 1)
- Pembrolizumab (category 1)
- Nivolumab + Ipilimumab
- For BRAF positive patients:
  - Dabrafenib + Trametinib (category 1)
  - Vemurafenib + Cobimetinib (category 1)
- Clinical trial

**Second-line or Subsequent**
- First-line options not already used or clinical trial
- Ipilimumab
- Dacarbazine or temozolomide
- High-dose IL-2
- Biochemotherapy
- Cytotoxic chemotherapy
- Imatinib for C-KIT mutated tumors

(Source: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Melanoma V.1.2017 © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed 04/18/2017.)
CTLA-4 and PD-1 Pathways

- Ipilimumab: inhibits CTLA-4 on the T-cells
- Pembrolizumab and Nivolumab inhibit PD-1 on the T-cells, preventing binding to PD-L1 on the tumor cells
- Ultimately, prevents immune system downregulation
# Comparison of Anti-PD-1 Agents

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial FDA Approval Date</strong></td>
<td>September 4, 2014</td>
<td>December 22, 2014</td>
</tr>
<tr>
<td><strong>Type of Antibody</strong></td>
<td>Humanized, IgG4 kappa immunoglobulin</td>
<td>Human, IgG4 kappa immunoglobulin</td>
</tr>
<tr>
<td><strong>Approved Dosing (single agent)</strong></td>
<td>2 mg/kg over 30 minutes every 3 weeks</td>
<td>240 mg IV over 60 minutes every 2 weeks</td>
</tr>
<tr>
<td><strong>Approved indication in unresectable or metastatic melanoma</strong></td>
<td><strong>Single agent</strong> in patients with unresectable or metastatic melanoma</td>
<td><strong>Single agent or in combination with ipilimumab</strong> in patients with unresectable or metastatic melanoma</td>
</tr>
</tbody>
</table>

Pembrolizumab and nivolumab package inserts 2017
## All Grade Autoimmune Toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Clinical Effects</th>
<th>Ipilimumab 3 mg/kg</th>
<th>PD-1 inhibitors</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash, vitiligo, pruritus</td>
<td>47-68%</td>
<td>13-26%</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, colitis</td>
<td>31-46%</td>
<td>14-19%</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Liver</td>
<td>Elevated enzymes, bilirubin, hepatitis</td>
<td>3-9%</td>
<td>1-4%</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypophysitis, hypothyroidism</td>
<td>4-6%</td>
<td>3-10%</td>
<td>After 9 weeks</td>
</tr>
</tbody>
</table>

• Black box warning for autoimmune effects, however neither ipilimumab, pembrolizumab or nivolumab lists any specific contraindications.

Case Presentation: DC

• DC is a 51-year-old male with rheumatoid arthritis who previously received certolizumab and now on prednisone 5 mg daily.

• He presents with newly diagnosed stage IV melanoma involving the liver.

• His tumor is BRAF wild-type (WT).

• Can we use a checkpoint inhibitor for DC’s metastatic melanoma?
Autoimmune Disorders and Cancer

• More than 80 distinct autoimmune disorders
  – Localized to specific organ systems vs. systemic
  – 3-8% of the US population estimated to have an autoimmune disorder

• Unclear whether the process of an autoimmune disease and/or the therapies can increase the risk of cancer
  – Chronic inflammation
  – Chronic immunosuppression

Ipilimumab in Autoimmune Diseases

-Retrospective review of 30 patients with advanced melanoma and pre-existing autoimmune disorders treated with ipilimumab
  - Rheumatoid arthritis (n=6)
  - Psoriasis (n=5)
  - Inflammatory bowel disease, lupus, multiple sclerosis or thyroiditis (n=2 for each) and other (n=7)
-43% were receiving autoimmune therapy concurrently
-27% had autoimmune exacerbations necessitating steroid therapy
-50% had no autoimmune flare or immune-related adverse events
-Overall response = 20% (1 patient with durable CR)

Anti-PD-1 Therapy in Autoimmune Diseases

- Retrospective trial of 52 melanoma patients with pre-existing autoimmune disorders treated with PD-1 inhibitors
  - Response rate = 33%
  - Flare requiring immunosuppression = 38%
    - Rheumatoid arthritis, polymyalgia rheumatica, Sjogren’s syndrome, psoriasis, and immune thrombocytopenic purpura
  - No flare was seen in patients with gastrointestinal (n=6) or neurological (n=5) disorders
  - Discontinuation due to flare = 2 patients

Patient Case: DC

• PD-1 therapy is indicated for first-line therapy for metastatic melanoma
• DC’s RA is well controlled
• Would consider single agent pembrolizumab or nivolumab with close monitoring
Conclusions

• Immunotherapy has revolutionized the treatment of melanoma, especially in the more advanced settings.

• Immune related adverse events are unique to this class of agents and require early recognition and treatment.

• Evolving retrospective data has shown the safety of using certain immunotherapies in select patients with autoimmune disease, though close monitoring is required.
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