Cutaneous Adverse Reactions to Melanoma Therapy: Immunotherapy Agents

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July 25, 2019
AAD Summer Meeting
New York, NY

**DISCLOSURES**
I do not have any relevant relationships with industry.

CTLA-4 inhibitor: ipilimumab
- Cytotoxic T-lymphocyte antigen-4 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit CTLA-4, which is a negative regulator of T-cell activation

Kandalaft et al., JCO 2011

PD-1 inhibitors: pembrolizumab and nivolumab
- Programmed cell death-1 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit PD-1, which plays an important role in downregulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance

Kandalaft et al., JCO 2011

**Checkpoint inhibitor skin reactions**
- Morbilliform eruptions
- Pruritus
- Vitiigo
- Psoriasis
- Eczema
- Disappearance of pigmented lesions
- Lichenoid dermatitis and mucositis
- Grover-like reactions
- Lupus-like reactions
- Erythema nodosum-like panniculitis
- Bullous pemphigoid and other autoimmune blistering diseases
- Granulomatous reactions
- Erythema multiforme and SJS/TEN-like reactions
- Alopecia areata

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Cutaneous adverse effects melanoma therapy
PD-1 inhibitor associated vitiligo may be associated with tumor response

Disappearance of pigmented lesions with PD-1 inhibitor therapy

A patient with fewer pigmented lesions on the skin 13 months following PD-1 inhibitor therapy initiation, compared to prior to treatment.

PD-1 inhibitor associated bullous pemphigoid

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C3d

PD-1 inhibitor associated bullous pemphigoid

• BP ELISA testing positive in our patients

Ipilimumab-related dermatitis herpetiformis

• 27 year old woman with Stage III melanoma, received adjuvant ipilimumab
• Developed asymptomatic pink papules near the elbows, back, buttocks 1 month after starting ipilimumab

Ipilimumab-related dermatitis herpetiformis

Mochel et al., J Cutaneous Path 2016

Grover-like reaction

Chen et al., J Cutaneous Path 2018

PD-1 inhibitor-associated lichenoid reactions

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How does discontinuation of immunotherapy affect melanoma outcomes?

PD-1 inhibitor infusion site sarcoidosis
Cutaneous adverse effects melanoma therapy

Delayed cutaneous adverse reactions to PD-1 inhibitors are frequently observed.

Cutaneous toxicities to PD-1 inhibitors are correlated to better melanoma responses:
- Late cutaneous toxicities (occurring > 3 months after beginning therapy) are correlated to better tumor responses than early cutaneous toxicities.
- Vitiligo and “rash” are correlated to better tumor response than pruritus.

Cutaneous adverse reactions may also occur after PD-1 inhibitor therapy has been discontinued.

Bullous erythema multiforme

Lupus-like cutaneous reaction to PD-1 Inhibitor

Shao et al, JCP 2017

Wang et al., JAMA Derm 2018
Bullous erythema multiforme

- Patient had a markedly delayed onset of cutaneous reaction attributable to pembrolizumab (38 months)
- Developed painful papules, plaques, and bullae on hands, and several oral mucosal erosions
- Resolved with course of prednisone but recurred with next cycle of pembrolizumab given

Alopecic areata in the setting of PD-1 / IDO inhibition

- 66 year old woman with metastatic melanoma, treated with PD-1 inhibitor and IDO inhibitor (UPCC 13514)
- Hairdresser started noticing areas of hair loss about 3 months after she started the medications

Alopecic areata in the setting of PD-1 / IDO inhibition

Alopecic areata induced by immune checkpoint inhibitors

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FDA approved medications for advanced melanoma

- Targeted kinase inhibitors
  - BRAF inhibitors (vemurafenib, dabrafenib, encorafenib)
  - MEK (trametinib, cobimetinib, binimetinib)
- Immunotherapy agents
  - Iplimimumab
  - PD-1 Inhibitors (nivolumab, pembrolizumab)
  - Talimogene laherparepvec/T-VEC
Talimogene Laherparepvec (T-VEC)

- Approved by the FDA in October 2015 for treatment of unresectable Stage IIIB, IIIC, or IV melanoma
- First in class oncolytic virus based on modified HSV-1
  - Injectable therapy, directed into tumor tissue
  - Modified via deletion of 2 nonessential viral genes
- Designed to selectively replicate in and lyse tumor cells while promoting regional and systemic antitumor immunity
  - Should not harm normal tissue

T-VEC = engineered HSV-1

<table>
<thead>
<tr>
<th>Genetic modification</th>
<th>Result</th>
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<tbody>
<tr>
<td>deletion of ICP34.5</td>
<td>prevents HSV infection of non-tumor cells, providing tumor-selective replication</td>
</tr>
<tr>
<td>deletion of ICP47</td>
<td>enables antigen presentation enhancing anti-tumor immune response by recruiting and stimulating dendritic cells to tumor site</td>
</tr>
<tr>
<td>insertion of GM-CSF gene (behind CMV promoter)</td>
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Proposed mechanism of action of T-VEC

- T-VEC selectively replicates in tumor cells and lyases them → release of progeny virus and tumor-derived antigens (TDAs)
- T-VEC modified to include 2 copies of human GM-CSF → promotes maturation and function of dendritic cells → activate anti-tumor T-cells through presentation of processed TDAs

Our patient

- Following treatment with T-VEC, biopsy of pigmented macules revealed no residual melanoma
- A neutrophil-rich dermal inflammatory infiltrate is suggestive of a Sweet’s like reaction, and may be attributable to the GM-CSF component of T-VEC

T-VEC associated granulomatous reactions

Septal and lobular panniculitis after T-VEC

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