Skin Deep Into Toxicities of Cancer Therapies

Mario E Lacouture MD
Member, Memorial Hospital
Director, Oncodermatology Program
New York, NY
Targeting the Immune System in Cancer….
And Targeting the Immune System in Skin

Epidermis

- Macrophages

Superficial dermis

- T cell
- Mast cells
- DDC

Deep dermis

- Vessels

Tong et al, *J Invest Dermatol* 2015
Immunotherapy and Rash: Increased Attention

Pubmed 2007-2015
(rash ± nivo or ipi or atezo or pembro)
Adverse Events to Immunotherapies: Oncologist

Nivolumab (n=474)

- **Skin** (n = 155; 33%): 5.0 (0.1–57.0)
- **Gastrointestinal** (n = 66; 14%): 7.7 (0.1–37.6)
- **Hepatic** (n = 19; 4%): 7.7 (2.0–38.9)
- **Pulmonary** (n = 9; 2%): 8.9 (3.6–22.1)
- **Endocrine** (n = 36; 8%): 10.4 (3.6–46.9)
- **Renal** (n = 8; 2%): 15.1 (3.9–26.4)

Weber et al. ASCO 2015
### AE type

<table>
<thead>
<tr>
<th>AE type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic keratosis</td>
<td>11 (13.4%)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>14 (17.1%)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>5 (6.1%)</td>
</tr>
<tr>
<td>Hypopigmented nevus</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Infections (tinea/herpes zoster/cellulitis)</td>
<td>7 (8.5%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>9 (11.0%)</td>
</tr>
<tr>
<td>Lichenoid reaction</td>
<td>14 (17.1%)</td>
</tr>
<tr>
<td>Primary melanoma</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>Cutaneous metastatic melanoma</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td>New nevus</td>
<td>5 (6.1%)</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>11 (13.4%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>5 (6.1%)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>12 (14.6%)</td>
</tr>
<tr>
<td>None</td>
<td>42 (51.2%)</td>
</tr>
<tr>
<td>Others in 15 patients (18.3%)</td>
<td></td>
</tr>
<tr>
<td>Sebopsoriasis</td>
<td>1</td>
</tr>
<tr>
<td>Acute generalized exanthematous pustulosis</td>
<td>1</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1</td>
</tr>
<tr>
<td>Solar lentigo</td>
<td>2</td>
</tr>
<tr>
<td>Cyst</td>
<td>1</td>
</tr>
<tr>
<td>Wound</td>
<td>1</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
<td>1</td>
</tr>
<tr>
<td>Skin tag</td>
<td>1</td>
</tr>
<tr>
<td>Rosacea</td>
<td>1</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>2</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>1</td>
</tr>
<tr>
<td>Unidentified abdominal rash*</td>
<td>1</td>
</tr>
</tbody>
</table>

Hwang et al, JAAD 2015
Maculopapular Rash to Immunotherapies

• **Rash**
  - Ipilimumab: 19%
  - Nivolumab: 15% (34%)
  - Pembrolizumab: 21% (39%)

• **Treatments**
  - Oral Antihistamines
  - Steroids
  - Grade 1 (topical)
  - Grade 2/3 (topical/oral)

Lichenoid Rash (Dermatitis) to Immunotherapies

PD-1/PD-L1 inhibitors (n=20)

Lichenoid Dermatitis from PD-1 inhibition

Schaberg et al, J Cut Pathol 2016
Oral Lichenoid Mucositis from PD1/PD-L1 Inhibitors

- PD1 inhibitors
  - Nivolumab
  - Pembrolizumab

- Oral lichenoid mucositis
  - Sensitivity
  - Tenderness

- Treatment
  - Dexamethasone 3.3mg/5mL
  - Triamcinolone in orabase
  - Clotrimazole lozenges

Sibaud et al, JEADV 2017
Oral Lichenoid Mucositis from PD1/PD-L1 Inhibitors

- PD1 inhibitors
  - Nivolumab
  - Pembrolizumab

- Oral lichenoid mucositis
  - Sensitivity
  - Tenderness

- Treatment
  - Dexamethasone 3.3mg/5mL
  - Triamcinolone in orabase
  - Clotrimazole lozenges

Sibaud et al, JEADV 2017
Pruritus to Immunotherapies

- Incidence
  - Ipilimumab: 4%
  - Nivolumab: 17%
    - Ipi+Nivo: 33%
  - Pembrolizumab: 21%
  - Atezolizumab: 7%

Ensslin et al, JAAD 2014; Sanlorenzo et al, 2014
Santoni et al, 2015; Rosenberg et al, 2016
Vitiligo-like Depigmentation to Immunotherapies

Vitiligo-like to IT (n=8)

Vitiligo-controls (n=30)

Larsabal et al, JAAD 2016
Vitiligo-like Depigmentation to Immunotherapies

Larsabal et al, JAAD 2016
Immunotherapies: Cutaneous Toxicities are Good

Overall Survival

OS: Rash
(Log rank $P = 0.001$)

OS: Vitiligo
(Log rank $P = 0.012$)

Freeman-Keller et al, Clin Cancer Res 2015
Blistering Disorders from PD1/PD-L1 Inhibitors

- Incidence: 2.4% (n=82)
  - Tense bullae
  - Pruritus
  - Anti-BP180/230 Abs
  - Oral involvement

- Treatment
  - Steroids
  - MMF
  - Azathioprine

Infrequent ir DAE from PD-1 inhibition

Psoriasis (n=21)

Inverse Psoriasis on PD1i

Lacouture, unpublished; Bonigen et al, 2016; Sibaud et al, 2016
Infrequent ir DAE from PD-1 inhibition

Keratoacanthomas (n=4)

Rosacea (n=3)

Immunotherapy-related Granulomas

Melanoma-Ipi+Nivo
Foreign Body Granuloma

Bladder ca–Atezolizumab
Granuloma Annulare

Sarcoidosis

Cotliar et al, JAAD 2016
Alopecia reported in 1-1.6% (n=855)
  - Biopsy: CD4+ T cells, scant CD8+ T cells

- Areata (totalis, universalis)

- PD-L1 is expressed on the hair follicle dermal sheath cup cell

- Melanocyte-specific cytotoxic T cells in melanoma patients treated with ICI

Zarbo et al, Br J Dermatol 2016
64 year old woman  stage IV melanoma
  – Progressed on ipilimumab
  – Nivolumab x 2 cycles
  – Rash after 2 wks → TEN
  – Improvement w CsA+pred
  – No mucosal involvement
  – Renal impairment

Epidermal programmed cell death-ligand 1 expression in TEN associated with nivolumab therapy

- 50 year old woman stage IV melanoma
  - Ipilimumab+nivolumab cycle 1 rash improved w steroids
  - Nivolumab 3X
  - Rash→TEN
  - Desquamation+ target lesions >90%
  - Mucosal involvement

Vivar et al, *J Cut Pathol* 2017
A 63-year-old woman with stage IV melanoma who progressed on nivolumab.

- Vemurafenib cycle 1
- Rash after 10 days improved with topical steroids
- Continued vemurafenib (>70% BSA)
- Mucosal involvement
- IV methylprednisolone
# Ipilimumab ➔ Vemurafenib: Higher Skin Reaction Severity

## Ipilimumab ➔ vemurafenib patients (n=13)

**Table 1.** Patients with Stage IV Melanoma Harboring a *BRAF V600E* Mutation Treated with Vemurafenib after Receiving Ipilimumab.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Rash</th>
<th>No. of Days to Onset of Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grade 3</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Grade 3</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>Grade 3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Grade 1</td>
<td>Not reported</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Grade 1</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>Grade 1</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Grade 3</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>Grade 1</td>
<td>28</td>
</tr>
<tr>
<td>12</td>
<td>No</td>
<td>28</td>
</tr>
<tr>
<td>13</td>
<td>No</td>
<td>28</td>
</tr>
</tbody>
</table>

Rechallenge possible after interruption

PD-1 inhibitor Serious DAE: Stevens Johnson Syndrome

PD-1

SJS

Lichenoid dermatitis

PD-L1
PD-1 inhibitor DAE: Serious v non-Serious

- Genes upregulated
  - PD-1i rash
    - CCL27, NURR1, GNLY, FASLG, and PRF1
  - PD-1i rash and SJS/TEN
    - PI3, SPRR2B, GZMB, CXCL9, CXCL10, and CXCL11

Goldinger et al, CCR 2016
Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies

**Grade**

1. Macules/papules covering <10% BSA*<br>   Asymptomatic or with symptoms**

2. Macules/papules covering 10–30% BSA*<br>   Asymptomatic or with symptoms**<br>   Limiting self-care ADL$*

3–4. Macules/papules covering >30% BSA<br>   Asymptomatic or with symptoms**<br>   Severe/Life-threatening symptoms<br>   Generalized exfoliative/ulcerated/bullous rash

**Investigations**

- Mucocutaneous clinical examination
- Serum testing for liver, kidney function, tryptase, IgE levels
- Consider dermatology consult
- Consider skin biopsy

**Management**

- Continue Immunotherapy
- Topical corticosteroids (intermediate to high potency)
- Oral antihistamines for pruritus
- Oral prednisone 1mg/kg/day or equivalent
- Oral antihistamines for pruritus
- Hold immunotherapy
- Oral prednisone 1mg/kg/day or equivalent
- Oral antihistamines for pruritus

**Follow-up**

- Repeat skin exam
- If develops symptoms, treat as higher grade
- If improves to ≤ Grade 1, resume immunotherapy
- After symptoms improve, taper steroids over ≥1 month
- If rash does not improve after 12 weeks from last dose of therapy, discontinue immunotherapy
- If improves to ≤ Grade 1, taper steroids over ≥1 month
- If worsens in 48 hours, consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil) or supportive measures$
- If no improvement ≥12 weeks from last dose of therapy, discontinue immunotherapy

### Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor

<table>
<thead>
<tr>
<th>Maculopapular Rash</th>
<th>Pruritus</th>
<th>Vitiligo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentle skin care instructions and sun-protective measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroid bid <strong>AND</strong> Oral antihistamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue drug at current dose and monitor for change in clinical severity of AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reassess after 2 weeks (by healthcare professional); If reactions worsen or remain stable, proceed to next step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical corticosteroid bid <strong>AND</strong> Oral antihistamines <strong>AND</strong> Oral corticosteroids (Prednisone 0.5 mg/kg or equivalent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical moderate/high-potency corticosteroid bid <strong>AND</strong> Oral antihistamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reassess after 2 weeks (by healthcare professional); If reactions worsen or remain stable, counsel patient and encourage continuation of anticancer treatment (vitiligo): OR proceed to next step (pruritus, maculopapular rash)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerable Grade 2 or Grade ≥3</td>
<td>Dose modifications as per package insert: <strong>Topical corticosteroid bid</strong> <strong>AND</strong> Oral antihistamines <strong>AND</strong> Oral corticosteroids (Prednisone 0.5 mg/kg or equivalent)</td>
<td></td>
</tr>
<tr>
<td>Reassess after 2 weeks (by healthcare professional); If reactions worsen or remain stable, dose interruption or discontinuation of anticancer treatment as per package insert may be necessary (pruritus, maculopapular rash)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IgE as a Therapeutic Target for Pruritus

Maurer et al, NEJM 2013; Holgate et al, 2008; Yu et al, JAAD 2014

Therapy-refractory BP

Baseline

Omalizumab

A

Itch-Severity Score

Mean [SE] Weekly Itch-Severity Score

Therapy-refractory BP

Baseline

Omalizumab

A

B

Maurer et al, NEJM 2013; Holgate et al, 2008; Yu et al, JAAD 2014
IL-6 as a Therapeutic Target

MTP therapy in SJS/TEN (n=8)

Therapy-refractory SLE/UV

Baseline

Tocilizumab

A

B

C

D

Conclusions

• Key sentinel finding
  • Immunotherapies may result in greater severity of maculopapular rash and atypical SJS/TEN

• Key translational finding
  • Serum markers as predictors and prognosticators
  • Specific inhibition of CD8+ T cell and IL-6 with approved agents provides an opportunity for therapies

• The study of cutaneous reactions in oncology will increase in importance
  • Adjuvant studies
  • Combination therapies
  • Increasing use of immunotherapies