CUTANEOUS ADVERSE EFFECTS OF TARGETED THERAPY AND IMMUNOTHERAPY

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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DISCLOSURES

I DO NOT HAVE ANY RELEVANT RELATIONSHIPS WITH INDUSTRY.
Review cutaneous adverse effects of targeted therapy and immunotherapies

- Checkpoint Blockade Therapies
  - Anti-CTLA 4
  - Anti-PD-1
  - PD-L1 inhibitors

- Targeted Therapies
  - BRAF Inhibitors
  - MEK Inhibitors
  - C-KIT Therapy and Epidermal Growth Factor Receptor Inhibitors
  - Hedgehog Pathway Inhibitor
**IMMUNOTHERAPY**

**Checkpoint Blockade Therapies**

- **Anti-CTLA-4** *(cytotoxic T lymphocyte-associated protein 4)*
  - Ipilimumab

- **Anti-PD-1** *(programmed death-1)*
  - Pembrolizumab
  - Nivolumab
  - Cemiplimab

- **PD-L1 inhibitors** *(programmed death ligand-1)*
  - Avelumab
Role of CTLA-4 in immunoregulation

Without Immunotherapy

- MHC
- Peptide
- TCR
- CTLA-4

Inactivation of T-Cell

Tumor escape

With Immunotherapy

- APC
- CD80/86
- Anti-CTLA-4 antibody

Activation of T-Cell

Elimination of tumor cells

Soularue et al. Gut 2018;67:2056-2067
Role of PD-1 in immunoregulation

Without Immunotherapy

Without Immunotherapy

With Immunotherapy

Tumor cell

MHC Peptide

TCR

PD-L1

PD-1

Inactivation of T-Cell

Tumor escape

Activation of T-Cell

Elimination of tumor cells

Anti-PD-L1

Anti-PD-1

Soularue et al. Gut 2018;67:2056-2067
Pertinent history and comprehensive physical examination, including evaluation of all mucous membranes.

Rule out any other etiologies of skin problem:
- Infection
- an effect of another drug
- skin condition linked to another systemic disease or unrelated primary skin disorder.

Review full list of patient medications to rule out other drug induced cause for photosensitivity.

Review of systems:
- Pain
- Fevers
- Malaise/myalgias/arthralgias
- Ocular discomfort or photophobia
- Mucosal involvement (e.g. hoarseness, dysuria, sores or genital discomfort)
- Abdominal pain
A biologic checkup, including a blood cell count, CMP, hepatitis antibody tests, TB testing, etc.

Directed serologic studies if an autoimmune condition is suspected, such as lupus or dermatomyositis: a screening antinuclear antibody (ANA) test, SS-A/Anti-Ro, and SS-B/Anti-La if the rash is predominantly photodistributed or demonstrating photosensitivity

Skin biopsy +/- DIF

Consider following patients closely using serial clinical photography
Pembrolizumab

Nivolumab

Anti-CTLA-4

Ipilimumab

Anti-PD-1

Pembrolizumab

Nivolumab
Dermatologic Eruptions with Checkpoint Blockade

A Scaly papules on the chest

B Hypertrophic scaly papules and plaques on the leg

C Inflammation around seborrheic keratoses and scaly papules on the back
Dermatologic Eruptions with Checkpoint Blockade

D Pseudovesiculated papules on the palm
E Papules and plaques on the palm
F Erosions on the penis

Grade I–II events mainly affect the skin and GI, whereas grades III–V are mainly restricted to the digestive tract.

Cutaneous toxicities such as rash, pruritus, and vitiligo are by far the most common and the earliest to occur.

Cutaneous toxicities are reported in 30% to 50% of patients treated with ICPI.
Most AEs occur within 3–6 months

Pruritus can be severe and is the most common associated symptom.

Risk appears to be dose-dependent with anti-CTLA-4 antibodies (cumulative toxicities not observed with anti-PD1)
- A delayed effect can be seen up to 1 year after the start of anti-PD-1

- Endocrine abnormalities reported < 10%
- Our understanding of cutaneous toxicities stems mostly from the ipilimumab experience.

- Cutaneous toxicities are less frequently reported with anti-PD-1 agents (17% to 37%).

- Incidence of Grade 3/4 cutaneous toxicities is the same as with ipilimumab.
Lichenoid Mucocutaneous eruptions
Psoriasiform Eruptions

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Psoriasiform Eruptions

© Waikato District Health Board

www.dermnetnz.org/topics/pembrolizumab
Bullous Pemphigoid
SJS with Nivolumab
Development of cutaneous toxicity, especially rash and vitiligo, may correlate with response to ICPI therapy in patients with metastatic melanoma.

Vitiligo can present with varying clinical presentations

Time to onset varies greatly; vitiligo can appear months after treatment initiation

1 Brahmer et al. J Clin Oncol 2018;36(17):1714-1768
A prospective study evaluating pembrolizumab in patients with melanoma, objective response rate (ORR) was higher in patients who developed vitiligo than in those who did not (71% vs 28%)
A retrospective analysis of 148 patients with melanoma treated with nivolumab, survival benefit was reported in patients who developed rash (n = 64) or vitiligo (n = 19)

- Overall survival (OS) was significantly longer in patients who developed rash and vitiligo
- ORR was also significantly higher in patients with rash/ vitiligo
- Clinical and biological patterns of vitiligo-like lesions occurring in patients receiving anti-PD-1 therapies may differ from vitiligo.

- Vitiligo-like lesions appear in photoexposed areas with a specific depigmentation pattern consisting of multiple flecked lesions without Koebner phenomenon.

- No personal or family history of vitiligo, thyroiditis, or other autoimmune disorders.

Analysis of blood samples revealed increased C-X-C motif ligand 10 levels in serum of anti-PD-1 patients.

Analysis of skin samples associated with skin infiltration of CD8 T-cells expressing C-X-C motif receptor 3 and producing elevated levels of interferon-γ and tumor necrosis factor-alfa.
Regimentation Associated with Melanoma Relapse

A During nivolumab

B Eight months after stopping nivolumab

Nakamura et al. JAMA Dermatol. 2017;153(9):942-944
Nivolumab + Ipilimumab

- Rash and pruritus seen in up to 70% of patients

- Incidence of rash, fatigue, and hepatic toxicity increased in the nivolumab-plus-ipilimumab group than in the ipilimumab group

Anti-PD-1

Cemiplimab
A Patient in Phase 1 Study

Baseline

Week 6
B Patient in Phase 2 Study

Baseline

Week 8

Cemiplimab

- Rash and pruritus seen in 15-25%
- Erythema multiforme and Pemphigoid (9 of 534 patients)
- Most common adverse reactions were fatigue, musculoskeletal pain, & GI
- Recurrence of dermatologic reactions after re-initiation is possible
Anti-PD-L1

Avelumab
Avelumab

https://www.dermnetnz.org/topics/merkel-cell-carcinoma
Anti-PD-L1 immunotherapy with DUAL ENGAGEMENT of both the adaptive and innate immune systems

Restoring adaptive immunity

T cell-mediated immune response

T cell

PD-1 receptor

Avelumab

Engaging innate immunity

NK cell-mediated tumor cell lysis via ADCC

NK cell

Fcy receptor

Avelumab

Avelumab

NK cell, natural killer cell.

https://www.bavencio.com/hcp/moa
- Rash and pruritus seen in 10-20%
- Most common adverse reactions were fatigue, musculoskeletal pain, & GI
- Peripheral edema
- Lymphopenia, anemia, increased LFTs
- Patients and family caregivers should receive education about immunotherapies and the clinical profile of possible AEs before initiating therapy and throughout treatment and survivorship.

- There should be a high level of suspicion that new symptoms are treatment related.
Management Recommendations

DERMATOLOGIC ADVERSE EVENT(S)

Maculopapular rash

ASSESSMENT/GRADING

- Total body skin exam, including mucosa
- Assess for history of prior inflammatory dermatologic diseases
- Consider biopsy if unusual features

Mild (G1)

Moderate (G2)

Severe (G3–4)

MANAGEMENT

- Continue immunotherapy
- Topical emollient
- Oral antihistamine
- Treatment with moderate potency topical steroids to affected areas

- Consider holding immunotherapy
- Topical emollient
- Oral antihistamine
- Treatment with high potency topical steroids to affected areas AND/OR
- Prednisone 0.5–1 mg/kg/day

- Hold immunotherapy
- Treatment with high potency topical steroids to affected areas
- Prednisone 0.5–1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement)
- Urgent dermatology consultation
- Consider inpatient care
Management Recommendations

**DERMATOLOGIC ADVERSE EVENT(S)**

**ASSESSMENT/GRADING**

- Pruritus
  - Total body skin exam, including mucosa
  - Assess for history of prior inflammatory dermatologic diseases

**MANAGEMENT**

- **Mild (G1)**
  - Continue immunotherapy
  - Oral antihistamines
  - Treatment with moderate potency topical steroids to affected areas

- **Moderate (G2)**
  - Continue immunotherapy with intensified antipruritic therapy
  - Oral antihistamines
  - Treatment with high potency topical steroids to affected areas
  - Dermatology consultation

- **Severe (G3)**
  - Hold immunotherapy
  - Oral antihistamines
  - Prednisone/methylprednisolone 0.5–1 mg/kg/day
  - Consider GABA agonists (gabapentin, pregabalin)
  - Consider aprepitant or omalizumab for refractory cases
  - Urgent dermatology consultation
Understanding Immunotherapy Side Effects

Contact your healthcare professional right away if you think you may be experiencing...

- Brain inflammation (encephalitis)
  - Fever, confusion, changes in mood or behavior, neck stiffness, seizure, extreme sensitivity to light.

- Hormone gland problems (especially the thyroid, pituitary, adrenal glands, pancreas)
  - Persistent or unusual tiredness, extreme tiredness, weight loss or gain, rapid heartbeat, increased sweating, hair loss, constipation, diarrhea, or fainting.

- Kidney problems
  - Decreased amount of urine or blood in the urine.

- Skin problems
  - Rash, itching, blistering, painful sores or ulcers.

- Joint or muscle problems
  - Severe or persistent muscle or joint pain, severe muscle weakness.

- Eye problems
  - Blurry or double vision or other vision problems, eye pain or redness.

- Lung problems (pneumonitis)
  - New or worsening cough, shortness of breath.

- Liver problems (hepatitis)
  - Yellowing of the skin or the whites of the eyes, severe nausea, or vomiting, pain on the right side of the stomach area, dark urine, bleeding or bruising more easily than normal.

- Intestinal problems (colitis)
  - Diarrhea or more frequent movements than usual. stools that are loose or watery, severe stomach pain, cramps, or fever.

- Nerve problems
  - Numbness or tingling in hands or feet, unusual weakness in legs, arms, or face.

Name: ____________________________

Cancer Dx: ____________________________

I-O Agents ORVD: □ Checkpoint Inhibitor(s)  □ CAR-T  □ Vaccines  □ Oncolytic Viral Therapy  □ Monoclonal Antibodies

Drug Name(s): ____________________________

Immunotherapy Tx Start Date: ____________________________

Other Cancer Medications: ____________________________

Note: Immunotherapy Agents are NOT Chemotherapy and Side Effects Must Be Managed Differently (See Back)

Immunotherapy Card

Immune-mediated side effects*, common with checkpoint inhibitors vary in severity and may require referral and steroids. Patients have a lifetime risk of immune-related side effects.

*May present as nausea, diarrhea, abdominal pain, cough, fatigue, headaches, vision changes, etc... confer with oncology team before changing I-O regimen or starting side effect treatment.

Oncology Provider Name: ____________________________

Oncology Provider No.: ____________________________

Emergency Contact: ____________________________

Contact Phone No.: ____________________________
Managing Immune Checkpoint Inhibitor (ICPi) Related Adverse Events

**Pneumonitis**
No standard imaging appearance

**Hepatitis**
Never infliximab

**Endocrinopathies**
Replace hormones, check Q cycle

**Colitis**
Check lactoferrin to stratify

**Dermatitis**
Consider topical steroids

**Grade 1**
Continue ICPi therapy with monitoring

**Grade 2**
Suspend ICPi
Resume at grade 1

**Grade 3**
Suspend ICPi
High-dose corticosteroids

**Grade 4**
Permanent stop ICPi
High-dose corticosteroids

**High-Dose Corticosteroids**
Prednisone 1-2 mg/kg/d or methylprednisolone 1-2 mg/kg/d

**Pro Tip:** If symptoms do not improve in 48-72 hours of high-dose corticosteroid, infliximab may be offered (except hepatitis)

Taper steroids over at least 6 weeks
TARGETED THERAPY

Gene Mutations Therapy

BRAF inhibitors
- Vemurafenib
- Dabrafenib
- Encorafenib

MEK inhibitors
- Trametinib
- Cobimetinib
- Binimetinib

C-KIT
- Imatinib
- Nilotinib
BRAF inhibitors

Vemurafenib
Dabrafenib
Encorafenib

MEK inhibitors

Trametinib
Cobimetinib
Binimetinib
Vemurafenib associated with more cutaneous adverse effects than Dabrafenib

- More than 50% associated with rashes, photosensitivity, verrucous papulomas, and PPD

- Increased in number of Actinic Keratosis

- SCC/KA up to 30% of patients with Vemurafenib

MEK Inhibitors

- BRAF inhibitor is linked with acquired resistance occurring in half of the patients after ~6 months.

- MEK inhibitors assist in longer overall survival.

- Associated with more acneiform eruptions.

- Some data suggests that BRAF/MEK inhibitors may produce less adverse effects than BRAF inhibitors alone.

Heinzerling et al. ESMO Open 2019;4(3):e000491
HAND-FOOTSKIN REACTION

PHOTOSENSITIVITY REACTION AFTER SUN EXPOSURE

C-KIT Targeted Therapy

Imatinib
Nilotinib
- Rash and pruritus noted in 30%

- More common affects are hematologic and liver abnormalities (nilotinib > imatinib)

- Superficial edema and muscle cramps common with imatinib

- SJ S reported in 11 patients (over past > 50 years)
Anti-Epidermal Growth Factor Receptor Therapies

- Cetuximab
- Panitumumab
EGF, TGF-alpha

Gene transcription
Cell cycle progression

Cell proliferation
Inhibition of apoptosis
Angiogenesis
Migration, Adhesion, Invasion
Common Cutaneous Reactions to EGFRi

- Acneiform eruptions up to 70%
- Xerosis in 50%
- Nail changes in 20%
- Hair abnormalities and oral ulcers reported

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125084s0228lbl.pdf
A meta-analysis of 38 studies investigating Cetuximab vs Panitumumab

- Cetuximab was associated with more acne-like rash and paronychia
- Cetuximab was associated with fewer severe skin rashes

Petrelli et al. Oncology 2018;94(4):191-199
Hedgehog Pathway Inhibitors

Vismodegib
Common reported adverse effects:
- muscle spasms
- alopecia
- dysgeusia

SCC in 10%

Pruritus in 10%
SUMMARY
SUMMARY

**Immunotherapies**
- Anti-CTLA-4
- Anti-PD-1
- PD-L1 inhibitors

- Cutaneous and GI toxicities are most often reported.
- Anti-CTLA 4 typically manifests with more adverse effects compared to anti-PD-1.
- Development of rash and vitiligo, may correlate with response in patients with metastatic melanoma.
**Targeted Therapies**

**BRAF and MEK inhibitors**

- BRAF inhibitors more associated with rashes, photosensitivity, alopecia, hyperkeratotic growths (incl AK/SCC)

- MEK inhibitors present with acneiform eruptions
SUMMARY

**Targeted Therapies**
C-KIT

- C-KIT therapies are coupled with more hematologic abnormalities
- Rashes in about 1/3 of patients
EGFR inhibitors present with:
- acneiform eruptions
- xerosis
- paronychia
SUMMARY

Targeted Therapies
Hedgehog Inhibitor

- Associated with more non-dermatological symptoms:
  - Muscle spasms, alopecia, and dysguesia

- SCC development in 10%
THANK YOU

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### Addendum: Management Recommendations

#### Table 1: Cutaneous side effects observed during targeted therapy (BRAF and MEK inhibitors) and immunotherapy (CTLA-4 and PD-1 inhibitors) and their management.

<table>
<thead>
<tr>
<th>Target</th>
<th>Skin toxicity</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
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<td></td>
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<tr>
<td></td>
<td>Braun et al. (2018)</td>
<td></td>
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<tr>
<td><strong>BRAF inhibitors</strong></td>
<td></td>
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<tr>
<td>(i) Vemurafenib</td>
<td>Skin rash (maculopapular)</td>
<td>Topical steroids (clobetasol propionate); oral corticosteroids (prednisonone); oral antihistamines; emollient agents</td>
</tr>
<tr>
<td>(ii) Dabrafenib</td>
<td>Photosensitivity</td>
<td>Avoid sun (broad-spectrum sunscreens that cover UVA spectrum, protective clothing)</td>
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<tr>
<td></td>
<td>Palmarplantar hyperkeratosis</td>
<td>Urea cream; avoid friction</td>
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<td>Verrucal keratosis</td>
<td>Cryotherapy; monitor for changes suggestive of SCC; acitretin as a chemopreventive drug</td>
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<td>Squamous cell carcinoma, alopecia, and hair</td>
<td>Excision, minoxidil 2%</td>
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<td></td>
<td>modifications</td>
<td>Nonsteroidal anti-inflammatory drugs; oral steroids (prednisolone)</td>
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<td></td>
<td>Panniculitis</td>
<td>Dermoscopic monitoring; radical surgery for melanomas; education on photoprotection and self-skin examination Excision</td>
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<td>Melanocytic proliferation</td>
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<td>BCC</td>
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<td><strong>MEK inhibitors</strong></td>
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<tr>
<td>(i) Trametinib</td>
<td>Acneiform rash (papulo-pustular)</td>
<td>Topical antibiotics (clindamycin, erythromycin); oral antibiotics (doxycycline, monocycline); topical steroids (prednicarbate); oral steroids (prednisone); oral antihistamines; oral isotretinoin Excision</td>
</tr>
<tr>
<td>(ii) Cobimetinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CTLA-4 inhibitors</strong></td>
<td>Rash (maculopapular, lichenoid eruption), eczema</td>
<td>Medium-to-high potency topical (and sometimes oral) corticosteroids; antihistamines</td>
</tr>
<tr>
<td>(i) Ipilimumab</td>
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<tr>
<td><strong>PD-1 inhibitors</strong></td>
<td>Vitiligo, psoriasis, autoimmune blistering disorders</td>
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<tr>
<td>(i) Nivolumab</td>
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<td>(ii) Pembrolizumab</td>
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