Adverse Cutaneous Reactions to Targeted Anti-Cancer Therapies

Jonathan Cotliar, MD
Clinical Associate Professor & Chief
Division of Dermatology
City of Hope National Medical Center
Disclosures

- Consultant for Xcovery
Objectives

• Discuss the role of the dermatologist in the care of cancer patients

• Recognize the diverse clinical presentation of adverse cutaneous reactions to traditional chemotherapeutic agents

• Recognize and treat cutaneous toxicities to targeted anti-cancer drugs
What is Oncodermatology?
Oncodermatology

- Expanding dermatology subspecialty
- Partnership with oncologists
- Availability
- Supportive care to facilitate cancer treatment
- Familiarity with spectrum of chemotherapeutics & targeted anti-cancer drugs and their associated cutaneous toxicities
Challenges in Oncodermatology

- Keeping patients on therapy
- Toxicities worse than cancer
- Inability to improve cutaneous toxicities
- Lack of dermatologists/ access
Chemotherapeutics

- **Alkylating agents**
  Classic: cyclophosphamide, ifosfamide, thiotepa
  Platinum agents: cisplatin, carboplatin, oxaliplatin

- **Antimetabolites**
  Analogs: cytarabine, fludarabine, cladribine, gemcitabine, pemetrexed
  Fluorouracil: 5FU, capecitabine, tegafur

- **Mitotic inhibitors**
  Taxanes: docetaxel, paclitaxel
  Vinca alkaloids: vincristine, vinblastine, vinorelbine
  Macro cyclic analogue: eribulin

- **Antitumor antibiotics**
  Anthracyclines: doxorubicin, daunorubicin
  Bleomycin

- **Topoisomerase inhibitors**
  Topoisomerase I: topotecan, irinotecan
  Topoisomerase II: etoposide, teniposide, amsacrine
# Targeted anti-cancer agents

## Monoclonal Antibodies
- Rituximab
- Trastuzumab
- Alemtuzumab
- Cetuximab
- Bevacizumab
- Panitumumab
- Ofatumumab
- Pertuzumab
- Obinutuzumab
- Ramucirumab
- Siltuximab
- Dinutuximab
- Darzalex/daratumumab
- Elotuzumab
- Ibritumomab tiuxetan
- Tositumumab
- Brentuximab
- Ado-trastuzumab

## Immunomodulatory Drugs
- Thalidomide
- Lenalidomide
- Ipilimumab
- Pomalidomide
- Binatumomab
- Pembrolizumab
- Nivolumab

## Signal Transduction Inhibitors
- Imatinib
- Gefitinib
- Trametinib
- Erlotinib
- Sorafenib
- Dasatinib
- Sunitinib
- Lapatinib
- Temsirolimus
- Nilotinib
- Everolimus
- Pazopanib
- Vandetanib
- Vemurafenib
- Crizotinib
- Ruxolitinib
- Omacetaxine
- Belinostat
- Panobinostat
- Trabectedin

## Transcription/Translational Inhibitors
- Decitabine
- Vorinostat
- Romidepsin
- Omacetaxine
- Belinostat
- Panobinostat
- Trabectedin

## DNA Repair Inhibitors
- Olaparib

## Proteosome Inhibitors
- Bortezomib
- Carfilzomib
- Ixazomib
Toxic Erythema of Chemotherapy (TEC)
Toxic Erythema of Chemotherapy (TEC)
Bologna et al. JAAD 2008

- Overlap of reactions to chemotherapy
- Toxic effect on eccrine ducts, acrosyringium, epidermis
- Areas of involvement reflect high density of eccrine glands
- Shared histologic features
- Cytarabine, Cyclophosphamide, Anthracyclines, 5-FU, Capecitabine, Taxanes, Methotrexate
## Toxic Erythema of Chemotherapy (TEC)

<table>
<thead>
<tr>
<th>AraC (cytarabine) ears</th>
<th>Palmar-plantar erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgdorf's reaction</td>
<td>Palmar plantar (palmoplantar) erythrodysesthesia</td>
</tr>
<tr>
<td>Chemotherapy-associated eccrine reactions</td>
<td>Toxic acral erythema</td>
</tr>
<tr>
<td>Eccrine squamous syringometaplasia (chemotherapy-induced)</td>
<td>Toxic erythema of the palms and soles</td>
</tr>
<tr>
<td>Epidermal dysmaturation (chemotherapy-induced)</td>
<td>Intertriginous eruption associated with chemotherapy</td>
</tr>
<tr>
<td>Epidermal dystrophy (secondary to cytotoxic agents)</td>
<td>Intertrigo-like eruption (chemotherapy-induced)</td>
</tr>
<tr>
<td>Erythrodysesthesia</td>
<td>Flexural erythematosus eruption (following autologous PRSCT)</td>
</tr>
<tr>
<td>Acral erythema</td>
<td>Intertrigo dermatitis</td>
</tr>
<tr>
<td>Acral erythrodysesthesia</td>
<td>Neutrophilic eccrine hidradenitis (chemotherapy-associated)</td>
</tr>
<tr>
<td>Chemotherapy-induced acral erythema (CIAE or CAE)</td>
<td>Chemotherapy-induced hidradenitis</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>Drug-induced hidradenitis</td>
</tr>
</tbody>
</table>
TEC

- Hands, feet
- Flexural, intertriginous
- Painful or asymptomatic
- Desquamation
- Recurrent/ progressive

**Histologic features:**
- Keratinocyte dysmaturation, apoptosis, necrosis
- Vacuolar degeneration
- Eccrine squamous syringometaplasia

Toxic erythema of chemotherapy

Intertriginous eruption associated with chemotherapy

Flexural erythematous eruption

Intertrigo dermatitis

Neutrophilic eccrine hidradenitis

Epidermal dysmaturation

Toxic erythema of the palms and soles

Acral erythema

Burgdorf's reaction

Eccrine squamous syringometaplasia

AraC ears

Hand-foot syndrome

Palmar plantar erythema

Palmar plantar erythrodysesthesia

Chemotherapy-induced acral erythema

Chemotherapy-induced epidermal dystrophy
TEC Pearls

- Tender rather than pruritic
- Can develop late and last 2-3 weeks beyond tx
- Mistaken for acute GVHD
- Sometimes anatomic site trumps morphology
- Check dressings
- Pyridoxine (Vitamin B6)?
Pyridoxine (B6) for TEC?

- Ota et al. 2014- 60mg QD ineffective for HFS in CRC pts on capecitabine
- Braik et al. 2014- 100mg QD ineffective for HFS
- Myung et al. 2015- effective for tx HFS but not prophylaxis
- Chen et al. 2013- 400mg pyridoxine may be effective to prevent HFS
- Macedo et al. 2014- celecoxib efficacious for prophylaxis of HFS
Hand Foot Syndrome

- Subtype of TEC
- Prodrome of dysesthesia
- Painful, symmetric erythema, edema
- Blisters, erosions
Hand Foot Syndrome

- Acral erythrodysesthesias
- Chemotherapy-induced acral erythema
- Acral erythema
- Palmar-plantar erythema
- Palmar-plantar erythrodysesthesias
- Toxic acral erythema
- Toxic erythema of the palms and soles
Toxic Erythema of Chemotherapy: Hand Foot Syndrome subtype (HFS)
# How to grade HFS

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 Grading of Hand-Foot Syndrome

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)</td>
<td>Minimal skin changes (erythema, edema, or hyperkeratosis) without pain</td>
<td>Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental ADL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Severe skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care ADL</td>
</tr>
</tbody>
</table>

Abbreviation: ADL, activities of daily living.

<sup>a</sup>Data from the National Cancer Institute.<sup>11</sup>
Capecitabine-Induced Hand-Foot Syndrome Complicated by Pseudomonal Superinfection Resulting in Bacterial Sepsis and Death

Case Report and Review of the Literature

Fridolin J. Hoesly, MD; Sarah G. Baker, MD; Nilanthi D. Gunawardane, MD; Jonathan A. Cotliar, MD
Nail Toxicities
Nail Toxicities

- Taxanes, Anthracyclines, Capecitabine
  - Docetaxel 35%
  - Paclitaxel 44%

Nail Toxicities

• Treatment strategies:
  - Minimizing wet work, hand work
  - Refraining from manicures/pedicures
  - Vinegar soaks
  - Cold gloves?
  - Culture!!!
Secondary Nail Infections
Prevention/ Treatment of nail infections

- Suspect gram negative, fungal organisms
- Culture!!!
- Ciprofloxacin
- Examine prior to treatment
- Avoid manicures/pedicures
- Mupirocin, Cephalexin for Gram⁺
- Vinegar soaks QD-BID
  (1/2 cup warm H2O, 1/2 cup white vinegar)
Toxicities to targeted anti-cancer agents
Hand Foot Skin Reaction (HFSR)
Table 3. Cutaneous Adverse Effects of Targeted Therapies and Associated Kinase Inhibitiona,b

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Cabozantinib</th>
<th>Sorafenib</th>
<th>Sunitinib</th>
<th>Imatinib</th>
<th>Erlotinib, Gefitinib, Cetuximab</th>
<th>Vemurafenib, Dabrafenib</th>
<th>Trametinib, Selumetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase inhibition</td>
<td>VEGFR2, c-MET, RET, c-KIT, FLT3, Tie-2</td>
<td>VEGFR2/3, PDGFR, RAF (A,B,C), FLT3</td>
<td>VEGFR2, PDGFR, c-KIT, FLT3</td>
<td>Bcr abl, PDGFR, c-KIT</td>
<td>EGFR</td>
<td>BRAF</td>
<td>MEK</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hair or skin depigmentation</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Xerosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Scrotal erythema or ulceration</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Nail splinter hemorrhage</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Paronychia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Facial erythema</td>
<td></td>
<td>+</td>
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<td></td>
<td>+</td>
</tr>
</tbody>
</table>
Multikinase inhibitors (MKIs) that cause HFSR

- Sorafenib - VEGFR, PDGFR, C-raf, B-raf - Renal Cell Ca, Hepatocellular Ca
  HFSR 34%

- Sunitinib - VEGFR, PDGFR, c-KIT, FLT3, RET, G-CSF1R - Renal Cell Ca, GIST
  HFSR 19%

- Pazopanib - VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, c-KIT - Renal Cell Ca, soft tissue sarcoma
  HFSR 4.5%

- Regorafenib - VEGFR, TIE-2, KIT, REF, RAF-1, BRAF, PDGFR - Colorectal Ca, Hepatocellular Ca, GIST
  HFSR 61%

- Axitinib - VEGFR-1, VEGFR-2, VEGFR-3 - Renal Cell Ca
  HFSR 29%

- Cabozantinib - VEGFR-2, c-MET, RET - Medullary Thyroid Ca
  HFSR 54%

- Vemurafenib, Dabrafenib - BRAF - melanoma
  HFSR 10-20%

- Lapatinib - dual TKI (HER2/neu, EGFR) - Metastatic Breast ca
Sunitinib
Sorafenib
Cabozantinib
Regorafenib
Axitinib
Sorafenib
What’s the difference?

Hand Foot Syndrome

Hand Foot Skin Reaction
What’s the difference?
# What’s the difference?

## Table 2. Comparison of Hand-Foot Syndrome and Hand-Foot-Skin Reaction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hand-Foot Syndrome</th>
<th>Hand-Foot-Skin Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequently implicated drugs</td>
<td><strong>Capecitabine, cytarabine, doxorubicin, 5-fluorouracil, taxanes</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td><strong>Sorafenib, sunitinib (multikinase inhibitors)</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| Histopathologic findings | Hyperkeratosis, parakeratosis  
Spongiosis  
Focal vacuolization and pyknosis in basal cell layer  
Dermis with ectatic blood vessels, mild perivascular lymphohistiocytic infiltrate<sup>4,15,16</sup> | Hyperkeratosis, parakeratosis  
Well defined horizontal zone of keratinocyte necrosis and discohesion (distinct from basal vacuolization or scattered pyknotic cells often seen in hand-foot syndrome)  
Dermis with ectatic blood vessels, mild perivascular lymphohistiocytic infiltrate with or without eosinophils in dermis<sup>15,17</sup> |
| Clinical appearance | Edema, erythema, and scale with or without blisters and erosions<sup>4,5</sup> | Scale with surrounding erythema progressing to hyperkeratosis, with or without blisters and erosions<sup>6,18</sup> |
| Distribution | Symmetrical and diffuse over the palms, soles, and digits<sup>4,5</sup> | Localized to pressure-bearing or flexural areas on palms and soles<sup>6</sup> |
| Onset | 24 h to 10 mo after initiation of therapy<sup>2,4</sup> (median, 79 d<sup>12</sup>) | Within 45 d of initiation of therapy in >95% of cases<sup>6</sup> |
How to treat HFS/HFSR

- Minimizing hand/foot use
- Orthotics, cotton socks, avoid tight-fitting shoes, running
- Emollients
- Keratolytics - urea
- High-potency topical steroids
- Topical anesthetics
- NSAIDs, GABA agonists, opioids
- Pyridoxine (B6)
- Cold gloves
- Celecoxib
- Vit E

- Stop anti-cancer drug/ dose reduction
Targeted agents for melanoma
BRAF Inhibitors

- Metastatic or unresectable melanoma
- Vemurafenib, Dabrafenib
- Fatigue, arthralgias, nausea, diarrhea, AKI
BRAF Inhibitors

- 74% develop skin toxicity
- Rash in nearly 18-27% (dose-dependent)
- Erythema, morbilliform, papulopustular, KP-like
- Verruca
- Eruptive KA, SCC- 20%
- Warty dyskeratoma
- Grover’s disease
- Wild-type melanoma
- Nevi
- Hand-foot-skin reaction
- Photosensitivity- 42%
- Keratosis pilaris-like
- Pruritus
- Acneiform eruption
- Alopecia
- Panniculitis
Vemurafenib
Vemurafenib
MEK Inhibitors
MEK Inhibitors

- Trametinib - inhibits MEK1/MEK2 alone or w/ dabrafenib
- Cobimetinib (w/ vemurafenib)
- Selumetinib, Binimetinib

- Morbilliform eruption (dose-dependent) 46-74%
- Papulopustular eruption
  - decreased incidence in BRAF/MEK combo
- Xerosis
- Alopecia
- Paronychia
- Mitigate eruptive SCC from BRAF inhibitors

Jae Jung, MD, PhD
Checkpoint Inhibitors

http://www.nzmu.co.nz/anti-pd-1-inhibitors
Ipilimumab

- Fully human monoclonal antibody to cytotoxic T-lymphocyte antigen (CTLA)-4
- Approved for unresectable or metastatic melanoma
- Most common toxicities:
  - Rash
  - Pruritus
  - Diarrhea/colitis
  - earliest onset

http://www.nzmu.co.nz/anti-ctl-4-inhibitors
Ipilimumumab

- Incidence of Derm AEs 44%
- High-grade 2.4%
- Pruritus
- Morbilliform, reticulated, erythematous, papular, sarcoidal
- Vitiligo (favorable prognosis)
- Perivascular lymphocytes, eosinophils
- Reactive treatment with topical/systemic steroids, antihistamines

Ipilimumab

Morbiliform

Papular
Management of rash associated with ipilimumab

**DETERMINE SEVERITY OF RASH**

**Grade 1/2**
- Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)
- Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness)
- Topical corticosteroids and oral antihistamines
- Resume ipilimumab if dermatitis resolves or improves to mild (localized) symptoms and systemic steroid dose is 7.5 mg prednisone equivalent or less

**Grade 3**
- Macules/papules covering >30% BSA with or without associated symptoms
- Hold ipilimumab
- Oral corticosteroids (1 to 2 mg/kg/day)
- IF SYMPTOMS WORSEN, SEE BELOW

**Grade 4**
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- Permanently Discontinue Ipilimumab
- Administer systemic corticosteroid therapy of 1 to 2 mg/kg/day of prednisone or equivalent
- When dermatitis is grade 0/1, corticosteroid tapering should occur over a period of at least 1 month

Management of skin pruritus associated with ipilimumab

**Pruritus Mild or Localized**
- Topical corticosteroids, antipruritics

**Intense or Widespread - Intermittent**
- Skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts);
  - topical corticosteroids and oral antihistamines indicated;
  - limiting instrumental ADL

**Intense or Widespread - Constant**
- Limiting self-care ADL or sleep;
  - oral antihistamines and corticosteroids indicated,
  - consider gabapentin, pregabalin, mirtazapine, aprepitant

PD-1, PD-L1 Inhibitors
PD-1 Inhibitors

- Nivolumab - melanoma, NSCLC, RCC, HL
- Pembrolizumab - melanoma, NSCLC, H&N SCC
- Fatigue
- Pyrexia, chills, infusion reactions
- Diarrhea/colitis
- Hypophysitis
- Hypo/hyperthyroidism
- Adrenal insufficiency
- Hepatitis
- Pneumonitis
- Myasthenia gravis
- Uveitis
- Interstitial nephritis
- Pancreatitis

PD-1 Inhibitors and Skin Toxicity

- 42% Pembrolizumab pts w/ skin AEs
  Morbilliform
  Papulopustular
  Pruritus
  Hypopigmentation
  Alopecia


Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: A single-institution cohort

Shelley Ji Eun Hwang, MBBS (Hons),*## Giuliana Carlos, MBBS,*## Deepak Wakade, MD,*## Karen Byth, PhD,*## Benjamin Y. Kong, MBBS,* Shaun Ghou, MBBS,* Matteo S. Carlino, MBBS, FRACP,*## and Pablo Fernandez-Penas, MD, PhD, FACD*##

Sydney, Australia

- 82 patients
- 40/82 (49%) developed adverse skin events
- Unclear if adverse events surrogate markers of efficacy

Table 1. Number of patients who developed a skin lesion

<table>
<thead>
<tr>
<th>Cutaneous adverse reactions</th>
<th>No. of patients, n = 82</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><strong>Lichenoid reaction</strong></td>
<td><strong>14 (17.1%)</strong></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><strong>Vitiligo</strong></td>
<td><strong>12 (14.6%)</strong></td>
</tr>
<tr>
<td>None</td>
<td>42 (51.2%)</td>
</tr>
</tbody>
</table>

Others in 15 patients (18.3%)
- Seboporiasis
- Acute generalized exanthematous pustulosis
- Photosensitivity
- Solar lentigo
- Cyst
- Wound
- Keratosis pilaris
- Skin tag
- Rosacea
- Psoriasis
- Hemangioma
- Livedo reticularis
- Unidentified abdominal rash

*
PD-1 Inhibitors and Psoriasis
PD-1 Inhibitors and Psoriasis
PD-1 Inhibitors and Psoriasis

Pembrolizumab

Nivolumab


Pembrolizumab and Hypertrophic Lichen Planus
Pembrolizumab and Sarcoidosis
Hedgehog pathway Inhibitors

(a) Hedgehog activation

- PTCH1
- Signal
- SMO
- GLI
- PTCH, GLI1

(b) Vismodegib

Chemical structure:

2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide; C_{19}H_{14}Cl_{2}N_{2}O_{3}S; M_r = 421.30

Nature Reviews | Drug Discovery
Hedgehog pathway Inhibitors

- Vismodegib, Sonidegib
- Metastatic BCC or locally advanced that can’t be tx with surgery/XRT
- 25% serious adverse events
- Leg cramps/muscle spasms (68%)- amlodipine, Gatorade, Mg
- Alopecia (10-63%)- minoxidil
- Dysgeusia (23-57%)- zinc, Synsepalum dulcificum (“miracle fruit”)
- Fatigue
- Nausea
- Diarrhea
- KA/SCC?
Vismodegib
Conclusions

• Oncodermatology will continue to grow

• Universal nomenclature is important

• Dermatology participation in pilot studies, grading schema, management of cancer pts is vital

• Be aware of autoimmune dermatoses from PD-1 inhibitors
Dermatology at City of Hope

• Oncodermatology clinic
• Primary care dermatology
• Inpatient consult service

• Multidisciplinary GVHD clinic
• Multidisciplinary Cutaneous lymphoma clinic
• Cutaneous Immunotherapy clinic
• Dermatopathology
• Oncodermatology fellowship

jcotliar@coh.org