Skin toxicities from cancer treatments

Resident Power Hour

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Topics Covered

• Skin toxicities of:
  • Chemotherapy
  • Targeted therapies
  • Immunotherapy
• Common skin toxicity syndromes
  • Hand-foot syndrome
  • Hand-foot skin reaction
  • Papulopustular (acneiform eruption)

Sources: Literature Review

• JAAD CMEs
• JAMA Derm Case series
• Case reports
• Meta-analyses
• Supportive Oncology journals
• Clinical trial publications (NEJM/JCO)

Outline

A 75 year old female with a large locally advanced BCC is started on vismodegib what side effect is she most likely to experience?

A) Diarrhea #7
B) Dysgeusia #3
C) Weight loss #4
D) Alopecia #2
E) Muscle spasms #1
F) Fatigue #5

Vismodegib: ERIVANCE trial

Table IV: Median time to onset of common adverse events in safety-evaluable patients

| Common aEs | Median (95% CI) of onset of event during treatment | Lowest % of patients with event developed for AE %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle spasm</td>
<td>48 (36.7-59.7)</td>
<td>4.8 (2.1-8.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (36.7-59.7)</td>
<td>4.8 (2.1-8.0)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>46 (34.9-57.5)</td>
<td>6.1 (3.0-10.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (23.7-46.2)</td>
<td>2.1 (0.8-4.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42 (30.5-53.7)</td>
<td>2.7 (1.3-4.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39 (27.5-50.5)</td>
<td>2.4 (1.3-4.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (35.5-58.0)</td>
<td>4.1 (2.1-6.3)</td>
</tr>
</tbody>
</table>

*Excludes common adverse events considered related to metastatic disease

Vismodegib

• Most common aEs that led to discontinuation (with n ≥ 2):
  • Muscle spasm, Weight decreased, Dysgeusia
  • AE caused tx discontinuation in 17.3%
  • AE typically occur within 6 months, if not they are unlikely to occur later on

Nail changes caused by chemotherapy and targeted therapies

<table>
<thead>
<tr>
<th>Paronychia</th>
<th>Onycholysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>EGFRi</td>
</tr>
<tr>
<td>mTORi</td>
<td>mTORi</td>
</tr>
</tbody>
</table>

A) Docetaxel: Taxane (microtubulin inhibitor) chemotherapy
B) Bevacizumab: VEGFi
C) Erlotinib: EGFRi
D) Everolimus: mTORi
E) Trametinib: MEKi

Which drug is not associated with paronychia?

A) Docetaxel: Taxane (microtubulin inhibitor) chemotherapy
B) Bevacizumab: VEGFi
C) Erlotinib: EGFRi
D) Everolimus: mTORi
E) Trametinib: MEKi

Sources:

Drug effects on distinct anatomic nail regions

Yellow discoloration: unique to sunitinib

Table 1. Treatment-related cutaneous adverse events in patients treated with sorafenib and sunitinib (p = 0.05)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients</th>
<th>Classic</th>
<th>RCC</th>
<th>GIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair discoloration</td>
<td>16</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Oral ulcerations</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Palmar-plantar hyperkeratosis</td>
<td>11</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sputum discoloration</td>
<td>17</td>
<td>10</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Oral discoloration</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nasal hyperkeratosis</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Black hyperkeratosis</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Oral erythema</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Yellow discoloration on nail

A patient presents with these skin color changes, what therapy is he likely receiving?

A) Sorafenib: MTKi  
B) Sunitinib: MTKi  
C) Imatinib: bcr-abl i  
D) Erlotinib: EGFRi  
E) Abiraterone: Androgen i

A patient with RCC presents with intense erythema and pain of the scrotum, what treatment is he likely receiving for his cancer?

A) Sunitinib: painful "toxic erythema"  
B) Everolimus: mucosal aphthous-like ulceration  
C) Sorafenib: reports of scrotal eczema  
D) Vemurafenib  
E) Imatinib

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Scrotal toxicities from TKI

- ONSET: “2 weeks after the initiation of therapy  
- Maximal intensity: “week 4  
- Disappears: during off weeks  
- Could reappear after reintroduction of the drug  
- Reports affecting labia majora as well

This side effect is most commonly reported with what cancer treatment?

A) Pembrolizumab  
B) Bortezomib  
C) Vemurafenib  
D) Imatinib  
E) Sunitinib
A patient was recently started on a cancer therapy and reported itching and redness at the site of prior radiation. What therapy is not associated with this reaction?

A) Tamoxifen
B) Methotrexate
C) Sorafenib
D) Erlotinib
E) Dacarbazine

Vemurafenib causes UVA-induced photosensitivity

A 68 YO F on vemurafenib for ovarian cancer present with the following eruption after spending time at an outdoor picnic. What is the etiology?

A) Radiation recall phenomenon
B) Photosensitivity
C) UV recall phenomenon

Vemurafenib causes UVA-induced photosensitivity

BRAF Inhibitors
Vemurafenib
Dabrafenib

Inflammatory/Disorders of abnormal cellular function
Photodynamic reaction
Neutrophilic eccrine hidradenitis
Photosensitive dermatoses
Pseudolymphoma

Abnormal epidermal function
Neutrophilic panniculitis
Neutrophilic eccrine hidradenitis
Planta hyperkeratosis (NHK)
Verrucous keratosis

Abnormal follicular epidermal function
Verrucous follicular erythema
Cyst/Milia-like lesions
Verrucous follicular acne
Curly hair regrowth

Design
Eruption new
Involuting
Changin nevi

Melanocytic
Neoplasm/Disorder of proliferation
Eruptive nevus
Melanoma
Verrucous keratosis
Degran hyperkeratosis

Melanocyte
Melanoma
SEG/NA

BRAF Inhibitors

Phototoxicity
Xerosis
Fissures
Planta hyperkeratosis (HFSR?)
Gingival hyperplasia
Telogen effluvium
Diffuse alopecia
Grey, Curly hair

LeBoeuf, J.

Mangold, et al.

Chu, et al.
JAAD 2012.
Most common side effects due to vemurafenib

"Rash"

- Grover-like eruption

Other "rashes"

- Darier-like
- Seborrheic dermatitis-like eruption
- Morbilliform


CombiDT Decrease incidences of:

- AK/SCC/KA
- Melanoma
- Hyperkeratosis
- Plantar hyperkeratosis
- Verrucal keratoses/VV
- Hair changes
- Grover's


<table>
<thead>
<tr>
<th>CombiDT Effect</th>
<th>No. (%) Decrease</th>
<th>Standard Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AK/SCC/KA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plantar hyperkeratosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verrucal keratoses/VV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grover's</td>
<td></td>
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</tr>
</tbody>
</table>

BRAF inhibitors can cause SCC/KA in 15-30% of patients due to which pre-existing mutation in lesional skin?

a) H-ras*
b) N-ras
c) Mutant BRAF
d) WT BRAF
e) c-kit
f) p53

~21-60% had Ras mutations
Hras is the most common mutation

Which of the following is not a feature of hydroxyurea?

A. Radiation sensitizer
B. Megaloblastic anemia
C. Pokikiderma of hands
D. Leg ulcers
E. Neurotoxicity
F. RA-like Inflammatory arthritis

Mechanism of Action: Impairs DNA synthesis
Inhibition of ribonucleotide diphosphate reductase (reduces nucleotides to deoxynucleotides)

Other cutaneous AE:
Photosensitivity
Radiation recall reactions
Alopecia
Dermatomyositis-like eruption
Drug-induced lupus
Lichenoid drug reactions
Hyperpigmentation of skin/nails

Neutrophilic Panniculitis (EN-like)

Most c/o cutaneous metastases
Early onset
mean 60d, median 24d
[7 days—16 months]

Drug-induced:
BRAF
NEX
BRAF + NEX
MTX (sorafenib/regorafenib)

Bleomycin known to cause:
A) Sclerodermatous changes
B) Flagellate hyperpigmentation
C) Raynaud’s phenomenon
D) Radiation recall
E) All of the above

Voriconazole is associated with increased incidence of:

A) Lentigines  
B) Melanoma  
C) Cutaneous SCC  
D) De novo nevi- not true  
E) A, B, and C  
F) All of the above  
G) A and C

Racette et al. JAAD 2005

A patient presents with a painful dermatitis after his initiating cancer treatment, which was made worse after using topical steroids. What agent is he likely on?

A. Capcitabine  
B. Docetaxel  
C. Sorafenib  
D. Temsirolimis  
E. Vemurafenib


Inhibition of mTOR pathway

The bad...
• Associated with skin fragility  
• Impaired epidermal barrier  
• Impair wound healing

The good...
• Reduced incidence in SCCs in patients with organ transplantation (preferred immunosuppressive agent in patients with high risk NMSC/numerous SCCs)

C. Larocca

A 35 YD M developed several painful papules and plaques on the trunk and extremities in the second week after initiation of induction chemotherapy with cytarabine for AML. What is the most likely diagnosis?

A. Panniculitis  
B. Leukemia Cutis  
C. Neutrophilic eccrine hidradenitis  
D. Cellulitis  
E. Sweet’s Syndrome

Bolognia, 3rd edition

Neutrophilic eccrine hidradenitis

Drugs:  
Cytarabine  
Anthracyclines  
Mitoxantrone  
Methotrexate  
Cyclophosphamide  
5-Fluorouracil  
Bleomycin  
Vinca alkaloids  
Imatinib mesylate  
Vemurafenib  
Can be polymorphic: linear, annular, EM-like +/- purpura


After 7 days of imiquimod for tx of AKs the patient developed painful erythematous annular plaques, fever, arthralgias and malaise. What is likely seen on skin pathology?

A. Neutrophilic dermatoses  
B. Vascular interface  
C. Spongiosis dermatoses

Imiquimod cutaneous autoimmune adverse events

- SLE-like changes
- Vitiligo
- Pemphigus foliaceus
- GVHD

**Mechanism:**

TLR 7 signaling increases interferon alpha signaling

(TLR/IFN alpha thought to be important in pathophysiology of SLE)

Chronic Arsenic

- Palmar-plantar keratoses
- Macular hypopigmentation
- Bowen's disease/NMSC

After treatment with ipilimumab a patient notes the development of several depigmented macules. She asks what this means?

**True or False?**

- Four times less risk of death in patients with vitiligo development compared with patients without vitiligo. TRUE
- Patient is at higher risk for developing other immune mediated AE FALSE

Intertriginous eruption

Often confused for infectious intertrigo

- Doxil
- Cytarabine
- 5-FU
- Cytosine arabinoside
- Etoposide
- MTX
- Busulfan
- Melphalan
- Carmustine
- Mitoxantrone

Vitiligo-like depigmentation from ICI is associated with improved PFS and OS in melanoma

Keratotic sole of foot

Diagnosis?

Wong et al. JAAD 1998

An Bras Dermatol 2010; Sept-Oct 2010

Wong et al. JAAD 1998

Eruptive KAs have been reported with all except:

A. Sorafenib  
B. Sunitinib  
C. Vemurafenib  
D. Pembrolizumab  
E. Dabrafenib

Neoplastic lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verrucous Keratoses</td>
<td>BRAFi</td>
</tr>
<tr>
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</tbody>
</table>

Inflammation of Actinic Keratoses

- 5-Fluorouracil
- Capecitabine
- Cisplatin
- Cytarabine
- Vincristine
- Docetaxel
- Dacarbazine
- Daclomycin
- 6-Thioguanine
- Pembrezole...

Management of taxane-induced scleroderma?

A. Permanent discontinuation of taxane
B. Transient discontinuation of taxane and dose reduction
C. Continue therapy and start systemic steroids and methotrexate
D. Continue therapy, but no effective therapy available

Scleroderma-Like Reaction to Taxanes

Precoced by edema

COX-2 inhibitors should be used for treatment of capecitabine induced hand foot syndrome.

- True

References:


Pseudocellulitis

Gemcitabine
Pemetrexed


Reactions on the Hands and Feet

Not all reactions on the hands and feet are the same

- Periarticular thenar erythema and onycholysis (PATERO)
  - Dorsal hand-foot syndrome
  - Thenar

- Hand-foot syndrome
  - Palmar-planter erythromyelobiosis
  - Acral erythema
  - Chemotherapy

- Hand-foot skin reaction
  - Targeted therapies
  - Callous and inflammation over sites of pressure and friction

Slide courtesy of N. Leboeuf

A patient on erlotinib presents with the following eruption 2 weeks after starting therapy. What would you use for treatment?

- A. Topical tazorac, topical clindamycin
- B. Topical hydrocortisone 1%, topical dapsone
- C. Topical triamcinolone, doxycycline
- D. Topical tretinoin, hydrocortisone, doxycycline
- E. Isotretinoin, topical triamcinolone, sunscreen

AVOID topical retinoids as they are irritating
Use topical steroids
Use topical clindamycin or oral doxycycline
Isotretinoin may be considered in severe cases

Hand foot skin reaction (HFSR) ≠ Hand foot syndrome (HFS)

<table>
<thead>
<tr>
<th>Skin toxicity</th>
<th>Cancer treatment</th>
<th>Histology</th>
<th>Localized features</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFSR</td>
<td>Targeted therapy</td>
<td>Handful of necrotic keratinocytes</td>
<td>Bucket hands and feet</td>
<td>Acral erythema and edema</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Erythrodysesthesia</td>
<td>Symptomatic hand and foot</td>
<td>Symptomatic hand and foot</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>Sub- or intra-epidermal or subcorneal blisters</td>
<td>Resolution with meprobamate</td>
<td>No resolution</td>
</tr>
</tbody>
</table>

Isotretinoin, topical triamcinolone, sun screen
Topical triamcinolone, doxycycline

Avoid topical retinoids as they are irritating

Isotretinoin may be considered in severe cases

Pruritus
Xerosis
Eczematous dermatitis
Psoriasis
Bullous pemphigoid
Cutaneous lupus
Lichenoid dermatitis
SJS/TEN
Morpiliform
Eruptive KA
Inflammation of SKs/AKs
Vitiligo
Vasculitis
Sweet’s syndrome

SKIN TOXICITIES

**Conclusion**

Hand foot skin reaction (HFSR) ≠ Hand foot syndrome (HFS)

- All reactions on the hands and feet are not the same

Slide courtesy of N. Leboeuf

Thank you!