SKIN TOXICITIES IN THE MANAGEMENT OF THE COLORECTAL CANCER PATIENT: DIAGNOSIS AND MANAGEMENT STRATEGIES

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This presentation is intended for HCPs ONLY
Nicole R. LeBoeuf, MD, MPH

Skin Toxicities from Immune Checkpoint Inhibitors

DISCLOSURES

Bayer: Speaker, Consultant
Seattle Genetics: Consultant

I will discuss the off label use of topical and systemic therapies for the management of dermatologic adverse events from cancer treatment.
AGENDA

• Introduction
• EGFR Inhibitor toxicities
• Dermatologic adverse events from checkpoint blockade
• Reactions on the hands and feet
• Life threatening reactions
INTRODUCTION
• “Connor’s case stresses...to all of us, how important the continuation of research is – to not only find ways to cure cancer, but ways to cure it humanely”.

Jennifer Shepherd Flanagan, Connor’s Mom

To learn more about Connor: http://connorflanaganfoundation.com/
THE SCOPE OF THE SKIN TOXICITY PROBLEM

High-grade = Grade 3 (severe) according to the NCI-CTCAE (National Cancer Institute’s Common Terminology Criteria for Adverse Events) v3.0 or V4.03 = ulcerative dermatitis or skin changes with pain interfering with function.

- Afatinib
- Axitinib
- Cabozantinib
- Cetuximab
- Dasatinib
- Erlotinib
- Everolimus
- Ipilimumab
- Lenalidomide
- Nilotinib
- Pazopanib
- Pertuzumab
- Regorafenib
- Sorafenib
- Sunitinib
- Temsirolimus
- Vandetanib

Percent of Patients With a Dermatologic Adverse Event

# THE SCOPE OF THE SKIN TOXICITY PROBLEM

<table>
<thead>
<tr>
<th>Drug</th>
<th>All Grade dAE %</th>
<th>High dAE %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>34.3</td>
<td>2.6</td>
<td>Drucker AM, et al. Eur J Haematol. 2013 Feb;90(2):142-50</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>88.2</td>
<td>11.3</td>
<td>Su X, et al. Oncology. 2009;77(2):124-33</td>
</tr>
</tbody>
</table>

dAE, dermatologic adverse event
132 adults who presented 2.5 years
   – 1 primary cancer type
   – Treated with 1 molecularly targeted agent

Outcome looked at standard billable costs to the patient for skin toxicity-related medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures

The 132 patients had a median of 3 clinic visits for management of skin toxicities

Median cost of $1920 per patient

Sorafenib-related dermatologic adverse events were the most costly to manage
   – Median cost of $2509 per patient

Impact and Management of Skin Toxicity Associated with Anti-Epidermal Growth Factor Receptor Therapy: Survey Results

- Effect on adherence, and on cancer therapy dosing
- A survey completed by 110 practicing US oncologists administering EGFR inhibitors demonstrated
  - 76% hold treatment due to rash
  - 60% reduced dose due to rash
  - 32% discontinued therapy secondary to the rash
  - 8% refer to a dermatologist

EGFR INHIBITOR IN COLORECTAL CANCER: ‘RASH’ & SURVIVAL/RESPONSE

OS, overall survival
CAPECITABINE-HFS IN CRC

• Capecitabine-induced HFS is associated with better PFS (Fig A) and OS (Fig B) in CRC patients

CRC, colorectal cancer; HFS, hand-foot-skin; HR, hazard ration; OS, overall survival; PFS, progression-free survival
OVERALL SURVIVAL IN PATIENTS WITH HCC TREATED WITH SORAFENIB: BY SKIN TOXICITY

Skin toxicities may be a surrogate marker for the treatment outcome

17 vs 6 months

HCC, hepatocellular carcinoma
The emergence of supportive oncodermatology: The study of dermatologic adverse events to cancer therapies

Burden
Dose
Adherence
Cost
Quality of life
Prognosis
EGFR INHIBITOR-INDUCED SKIN TOXICITIES
EGFR INHIBITOR:
PERIORIFICAL DERMATITIS-LIKE

Figures: LeBoeuf
EFFECT OF EGFRiS ON SKIN

- Four major alterations
  - Dry skin
  - Follicular inflammation
  - Bacterial super-infection
  - Sensitivity to ultraviolet radiation

EGFRiS, EGFR inhibitors
Figures: LeBoeuf
MANAGEMENT STRATEGIES

• Prevent bacterial superinfection
  – Minocycline/Doxycycline
  – Bleach baths
  – Clindamycin lotion if pustules

• Prevent ultraviolet radiation
  – Broad spectrum UVA/UVB SPF 30+ at all times
  – Physical blockers

• Minimize dryness
  – Bathe or shower in tepid water
  – Apply bland emollient (ointment or cream)

• Decrease follicular inflammation
  – Topical corticosteroid
  – Minocycline or doxycycline as an anti-inflammatory

UVA, Ultraviolet A; UVB, ultraviolet B; SPF, sun protection factor
Grade \( \geq 2 \) skin toxicities in the 6 week treatment period was 29% vs 62% for pre-emptive versus reactive group.

REACTING WORKS TOO
TOPICAL STEROID CLINICAL PEARLS

• Face/groin/breasts:
  – Class V/VI (Hydrocortisone 2.5%/desonide)

• Body:
  – Wide spread: Class III/IV
    • Triamcinolone 0.1% → 1 pound jar
  – Focal or more severe: Class I for 2 weeks at a time
    • Clobetasol
    • Halobetasol
    • Betamethasone dipropionate

• Palms and soles:
  – Class I (Clobetasol/halobetasol/betamethasone dipropionate ointment)
    – Monitor for or treat tinea preventatively

• Scalp:
  – Class I-III solution or foam (clobetasol/fluocinonide, etc).

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Ointments > Creams
>> Lotions

Ointments are thick and greasy

Foams or solutions for areas with dense hair
EGFRi: XEROSIS AND DERMATITIS
High potency topical steroids for inflammation
Skin glue for fissure pain
EGFRi: SUPERINFECTION

- Bleach baths: 1/4c in 40 gallon tub
- Mupirocin to crusts and nares

EGFRi, EGFR inhibitor.
Figure: LeBoeuf
EGFRi: TRICHOMEGALY

- Trim lashes to prevent corneal scratching
EGFRI: PARONYCHIA

- Culture if there is pus
- Oral TCN antibiotics
- Dilute vinegar soaks
- Topical high potency steroids

EGFRI, EGFR inhibitor; TCN, tetracycline
Figures: LeBoeuf.
EGFRi: PERIUNGUAL GRANULATION TISSUE

- Treat paronychia
- Silver nitrate for granulation tissue
- Tape to pull lateral nail fold away
- Wide toe box in shoes

EGFRi, EGFR inhibitor
Figure: LeBoeuf
PREVENTION & COUNSELING

• Start in everyone
  – Broad spectrum UVA/UVB SPF 30+ at all times
  – Topical corticosteroid daily to face, chest upper back
  – Bathe or shower in tepid water
  – Apply bland emollient (ointment or cream)

• Consider in everyone*
  – Minocycline or Doxycycline

UVA, Ultraviolet A; UVB, ultraviolet B; SPF, sun protection factor

“We propose that patients with a favorable gut microbiome (for example, high diversity and abundance of Ruminococcaceae and Faecalibacterium) have enhanced systemic and antitumor immune responses mediated by increased antigen presentation and improved effector T cell function in the periphery and the tumor microenvironment.”

Do we need to consider the effects of antibiotics on gut microbiome diversity and response to cancer therapy in GI Oncology?
DERMATOLOGIC ADVERSE EVENTS FROM CHECKPOINT BLOCKADE
“IMMUNOTHERAPY CAUSES

Misha Rosenbach, MD
Deputy Editor, JAMA Dermatology
T CELLS: COMMAND CENTRAL OF THE IMMUNE SYSTEM IN THE SKIN

DC, dendritic cell; FOXP3, forkhead box P3; IL, interleukin; IFN, interferon; ROR, related orphan receptor; STAT, Signal transducer and activator of transcription; TCR, T cell receptor; TGF, Transforming growth factor; T_{H1} cell; Type 1 T helper cell; T_{reg} cell, regulatory T cell

Slide Courtesy of Rachael Clark MD, PhD.
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Erythema multiforme
Lichenoid dermatitis
Eczematous
Psoriasiform
Morbilliform
Hand Foot Syndrome
Neutrophilic dermatoses
“and others”
### INFLAMMATORY “RASH”: WHAT TO DO?

**Grading**

<table>
<thead>
<tr>
<th>Grading</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.</td>
<td>Continue ICPi</td>
</tr>
<tr>
<td>G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic</td>
<td>Treat with topical emollients and/or mild-moderate potency topical corticosteroids. Counsel patients to avoid skin irritants and sun exposure.</td>
</tr>
<tr>
<td>G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis</td>
<td>Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1. Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks. In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids.</td>
</tr>
<tr>
<td>G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis</td>
<td>Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks.</td>
</tr>
<tr>
<td>G4: All severe rashes unmanageable with prior interventions and intolerable</td>
<td>Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) &lt; 10 mg. Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves.</td>
</tr>
</tbody>
</table>

*Initiate methylprednisolone (or equivalent) 1-2mg/kg, tapering over at least 4 weeks.*

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AE, adverse event; BSA, body surface area; CTCAE, common terminology criteria for adverse events; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event.

CLINICAL APPROACH TO THE ICI PATIENT WITH “RASH”

• Assess for signs of severe cutaneous adverse reaction (SCARs)

• Evaluate morphology, low threshold for biopsy

• Let the clinical exam and biopsy guide management

• Treat the toxicity in as targeted a way as possible
  – Knock out the components of the immune reaction leading to the irAE
  – Leave the rest of the immune system intact to respond to the malignancy

• Goal: Uncouple toxicity from therapeutic effect
CTLA4i-INDUCED TOXICITY

- Typically classified as maculopapular rash
  - 47-68% of patients
  - 1-4% severe
  - Onset 3-6 weeks

- 11% Vitiligo-like depigmentation
- 29% Pruritus

- Rare reactions
  - Cutaneous sarcoidosis
  - Sweet syndrome, Pyoderma gangrenosum-like
  - Dermatomyositis
  - DRESS syndrome
  - Radiation recall
  - Phototoxicity
  - Acneiform eruption
  - Prurigo

CTLA4i, Cytotoxic T Lymphocyte-Associated Antigen 4 inhibitor; DRESS, Drug reaction with eosinophilia and systemic symptoms
MACULOPAPULAR RASH

## APPROACH TO MACULOPAPULAR RASH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Management</th>
<th>Specialist referral?</th>
</tr>
</thead>
</table>
| 1     | Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Topical steroids  
Antihistamines  
No dose modification |                     |
| 2     | Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL | Non-acute dermatology referral  
Topical steroids + antihistamine  
Consider oral steroids if rapidly progressive  
- Rule out systemic hypersensitivity: CBC with differential, CMP, UA  
- Prednisone 0.5 – 1mg/kg/day | ✔️ |
| 3     | Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL | Refer for dermatology consult  
Rule out systemic hypersensitivity: CBC with differential, CMP, UA  
Consider systemic steroids if rapidly progressive or unresponsive to topical steroids: Prednisone 0.5 – 1mg/kg/day until rash resolves to ≤ Grade 1 | ✔️ |
# APPROACH TO MACULOPAPULAR RASH

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<tr>
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<th>Description</th>
<th>Management</th>
<th>Specialist referral?</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Macules/papules covering &lt;10% BSA with or without symptoms (e.g., pruritus, burning, tightness)</td>
<td>Topical steroids</td>
<td>No dose modification</td>
</tr>
<tr>
<td>2</td>
<td>Macules/papules covering 10–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
<td>Topical steroids + antihistamine. Consider oral steroids if rapidly progressive; Rule out systemic hypersensitivity: CBC with differential, CMP, UA</td>
<td>Non-acute dermatology referral</td>
</tr>
<tr>
<td>3</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting self care ADL</td>
<td>Refer for dermatology consult. Rule out systemic hypersensitivity: CBC with differential, CMP, UA. Consider systemic steroids if rapidly progressive or unresponsive to topical steroids. Prednisone 0.5 – 1mg/kg/day until rash resolves to ≤ Grade 1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**How extensive is the eruption?**
**How rapid is the pace of spread?**
**How symptomatic?**
**Is there skin tenderness, mucosal involvement or blisters?**
**Is there any evidence of systemic hypersensitivity?**
IPILIMUMAB-INDUCED SWEET SYNDROME

Prednisone, with colchicine.
Figure: LeBoeuf
PD1i/PDL1i-INDUCED SKIN REACTIONS

• 13-49% of patients
• Pruritus
• Exacerbation of pre-existing dermatoses
  – Rosacea, atopic dermatitis
  – Psoriasis, lupus
  – Inflamed keratoses
• New autoimmune-like diseases
• Recurring reaction patterns
  – Bullous disorders
  – Psoriasiform eruptions
  – Lichenoid eruptions

PD-1i-INDUCED: ALOPECIA AREATA UNIVERSALIS

Figure: LeBoeuf
PD-1i-INDUCED: VITILIGO-LIKE DEPIGMENTATION

Figure: LeBoeuf
PD1i-INDUCED: SWEET SYNDROME

Prednisone
Dapsone

Courtesy of Cecelia Larocca, MD.
PD1i-INDUCED: SUBACUTE CUTANEOUS LUPUS

Betamethasone dipropionate ointment, hydroxychloroquine 200mg BID
No PD1 Inhibitor interruption, no systemic prednisone

BID, twice a day
Courtesy of Ashleigh Eberly PA-C.
SELECT REACTION PATTERNS FROM PD1/PDL1 BLOCKADE
81 YEAR OLD MAN WITH LUNG CANCER AND BLISTERS

- After 40 cycles (19 months) developed blisters on 4-5% BSA
- Biopsy, DIF, IIF consistent with bullous pemphigoid
- Lung cancer, complete response by this time

BSA, body surface area; DIF, Direct immunofluorescence; IIF, indirect immunofluorescence
Figure: LeBoeuf
Indirect Immunofluorescence: BP180 and desmoglein 3 +.


Figure: LeBoeuf
PD-1 INHIBITOR: BULLOUS PEMPHIGOID

- Prolonged prednisone tapers per oncology
  - Hospitalized for delirium
  - Compression fractures
  - Persistent bullae

- Rituximab
  - 4 weekly doses (375mg/m²)
  - Complete response and remission of bullae

- Stable malignancy at 2 years


Figure: LeBoeuf
ICI INDUCED BULLOUS PEMPHIGOID – YALE

- 7 of 853 patients at Yale developed bullous pemphigoid (yearly incidence 0.4%) after treatment with anti-PD1/PDL1
- Mean latency to onset 6.25 months
- 4 Lung, 1 melanoma, 1 urothelial, 1 RCC
- 4 Males, 3 females

- 7 of 7 BP patients received systemic corticosteroids

BP, bullous pemphigoid; ICI, immune checkpoint inhibitor; RCC, renal cell carcinoma
ICI INDUCED BULLOUS PEMPHIGOID – DFCI

- 12 of 2816 patients at DFCI (yearly incidence 0.1%) who developed BP after first PD1/PDL1 inhibitor therapy
- Mean latency to onset was 8.5 months
- 6 Lung, 3 melanoma, 1 breast, 1 esophageal, 1 renal cell
- 9 Males, 3 Females

- 10/12 were treated with systemic steroids for BP
- 4 Patients had non-bullous variant

BP, bullous pemphigoid; DFCI, Dana-Farber Cancer Institute; ICI, immune checkpoint inhibitor; Singer S, et al. Unpublished Data.
PD1i-INDUCED NON-BULLOUS PEMPHIGOID

- Biopsy, DIF, IIF, ELISAs
- Failed topicals, doxycycline & nicotinamide
- IgE Elevated ➞ Omalizumab

DIF, Direct immunofluorescence; IgE, immunoglobulin E; IIF, indirect immunofluorescence

Figures: LeBoeuf
PD-1i-INDUCED BULLOUS PEMPHIGOID

- Onset between 6 weeks and 19 months
- Persistent disease despite treatment discontinuation
- BP180 as a potential common antigen
  - Limited number of cases
  - More than half negative
- Risk factors not yet clear


Figures: LeBoeuf
BULLOUS PEMPHIGOID MANAGEMENT: DERMATOLOGIST’S APPROACH

• First Line (<10% BSA)
  – **Topical high potency steroids**
  – Doxycycline 100mg BID + Nicotinamide 500mg BID
  – PO steroids 0.5-1mg/kg/d if symptoms severe or rapidly progressive

• Second Line:
  – Azathioprine – 0.5-2.5mg/kg/d
  – Mycophenolate mofetil – 1.5-3g/d
  – Dapsone (especially with mucosal involvement)
  – Methotrexate

• Third Line:
  – **Omalizumab**
  – **Rituximab**
  – IVIg
  – Cyclophosphamide
  – Cyclosporine
  – Etanercept
  – Plasmapheresis

• Patients OFTEN flare with taper of systemic steroids
• Requires prolonged steroid tapers when they are used
• BP is not the same as a cytotoxic bullous reaction

BID, twice a day; BP, bullous pemphigoid; BSA, body surface area; IVIg, intravenous immunoglobulin; PO, per os;
PD1i: PSORIASIS WITH INFLAMMATORY ARTHRITIS

Topicals, NSAIDs
Methotrexate 12.5mg qweek

Figures: LeBoeuf
PD-L1i-INDUCED PSORIASIS

Clobetasol
Acitretin 25mg daily

Figures: LeBoeuf
CTLA4i + PD1i-INDUCED PSORIASIS & ARTHRALGIAS

Figures: LeBoeuf
CTLA4i + PD1i-INDUCED PSORIASIS & ARTHRALGIAS

- Failed topical steroids, keratolytics, retinoids
- Prednisone taper required for joint symptoms
- Could not tolerate acitretin
- Challenges to UV: Vitiligo, h/o melanoma, cost, frequency

h/o, history of; UV, ultraviolet
Figures: LeBoeuf
APREMILAST 30MG BID

BID, twice a day

Figures: LeBoeuf
**PSORIASIS APPROACH**

Psoriasiform lesions while on checkpoint inhibitor:

- **Joint Symptoms?**
  - No: Topical steroids
    - Clinical control?
      - No: Phototherapy
      - Yes: Monitor
  - Yes: Methotrexate
    - Apremilast
      - with or without topicals
      - Clinical control?
        - No: Consider: IL-17/IL12/23
          - Mycophenolate mofetil
          - Cyclosporine
          - TNF-alpha inhibitor
          - Monitor
        - Yes: Monitor

- **Yes**: [Consider Rheumatology Consult]

**Systemic steroids are not part of the management of psoriasis except in rare cases of erythroderma.**

**Most psoriasis flares with taper of systemic steroids**

IL. interleukin

PD1i-INDUCED LICHENOID REACTIONS

- Most common specific eruption from PD1/PDL1 blockade
- Onset reported from 3 days to 12.8 months

- Among one cohort of 20 patients referred for “rash” 80% had red papules with scale
  - 94% had lichenoid interface dermatitis on pathology (regardless of clinical morphology)

“LICHENOID”

• Lichenoid is a clinical AND pathologic descriptor

• **Clinically:** Flat topped, red or purplish papules, sometimes with scale and Wickham’s striae

• **Pathologically:** Infiltrate of lymphocytes at the dermal-epidermal junction that may cause vacuolar change

Figures: LeBoeuf
PD1i-INDUCED LICHENOID REACTIONS

Topical steroids

Figures: LeBoeuf
PD1i-INDUCED BULLOUS LICHENOID ERUPTION

• Topical steroids
• Prednisone taper
• Acitretin 10mg --> 25mg daily

Figures: LeBoeuf
PDL1i-INDUCED LICHENOID ERUPTION

- Topical steroids
- Prednisone taper required by protocol
- Acitretin 10mg --> 25mg daily

Figures: LeBoeuf
ACITRETIN 25MG
LICHENOID ERUPTIONS: 
DERMATOLOGIST’S APPROACH

• First Line:
  – Topical/Intralesional steroids
  – Antihistamines

• Second Line:
  – Systemic retinoids (acitretin) – Starting 10mg daily, increasing to 25mg daily if not controlled at 6 weeks
  – nbUVB or PUVA
  – Metronidazole 500mg BID
  – Sulfasalazine (cutaneous; Ø mucosal) – 1.5-3g/d
  – Systemic steroids* – 15-20mg/d x 2-6 weeks then taper

• Third Line:
  – Hydroxychloroquine 200mg BID
  – TMP-SMX, Tetracycline, Griseofulvin (oral erosive), Itraconazole, Terbinafine, Cyclosporine
  – MMF (disseminated, erosive, hypertrophic, bullous and LPP)
  – Azathioprine
  – IFN
  – Topical tacrolimus
  – Thalidomide

*Systemic steroids only for temporary relief if severe, while adding steroid sparing agent
PROGNOSTIC SIGNIFICANCE OF DERMATOLOGIC ADVERSE EVENTS

Pembrolizumab PFS
n=83

Nivolumab OS
n=148

d(AE), dermatologic adverse events; PFS, progression-free survival; OS, overall survival
ALL irAEs, PROGRESSION FREE AND OVERALL SURVIVAL

irAEs, Immune-related adverse events; mPFS, median progression-free survival; mOS, median overall survival
All patients with high grade hypophysitis
Low Dose = 7.5mg or less
High Dose = 20mg or higher

LD, low dose; HD, high dose
Response rates when on baseline prednisone
Less than 10mg Versus 10mg or Higher

19% CR/PR vs 6%
18% CR/PR vs 8%

Efficacy of PD-(L)1 Blockade in Patients on Baseline Steroids

CR, complete response; PR, partial response; SD, stable disease; POD, progression of disease
STEROID SUMMARY

- While some debate remains about which irAEs are associated with response in which tumor types and patients, irAEs appear to be associated with response and survival benefit.

- Multiple studies now suggest that steroids mitigate effect in at least some populations and that dose and timing is important.

- Steroids should be used early and liberally in life-threatening toxicity and very judiciously in less severe toxicity.

- Steroids should be AVOIDED when treating disorders in which steroids would not otherwise be indicated.

irAEs, immune-related adverse events
REACTIONS ON THE HANDS AND FEET
NOT ALL REACTIONS ON THE HANDS AND FEET ARE THE SAME

Figures: LeBoeuf
REATIONS ON THE HANDS AND FEET

NOT ALL REACTIONS ON THE HANDS AND FEET ARE THE SAME

- **Dorsal hand-foot syndrome**
  - Taxanes

- **Hand-foot syndrome**
  - Palmoplantar erythrodysesthesias
  - Acral erythema

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

- **Immune mediated** disorders affecting the hands and feet
DORSAL HAND-FOOT SYNDROME

- Taxane-associated
- More common with multidrug therapy
- More common with weekly regimens
- Onset days to weeks
- Associated with nail lifting


Figures: LeBoeuf
TAXANES: DORSAL HAND-FOOT SYNDROME

Figures: LeBoeuf
## TOXICITY PREVENTION WITH FROZEN GLOVES

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Control Hands (N=45)</th>
<th>Frozen Glove-Protected Hands (n=45)</th>
<th>( p )</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Nail Toxicity</td>
<td></td>
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<tr>
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<td>49</td>
<td>34-64</td>
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<tr>
<td>Incomplete Data</td>
<td>9</td>
<td>3-21</td>
<td>9</td>
</tr>
</tbody>
</table>

Cl, confident interval
FROZEN GLOVES AND SOCKS

“Elasto-gel Chemotherapy Hypothermia Slippers and Mitts”

Source figures: amazon.com
http://iamnotcancer.blogspot.com/2012/07/on-finishing-chemotherapy.html
TAXANES: DORSAL HAND-FOOT SYNDROME

Before and after cooling with ice packs wrapped on feet but not toes

Figures: LeBoeuf
HAND FOOT SYNDROME

- Acral erythema/palmoplantar erythrodysesthesia (PPE)
- Seen most commonly with capecitabine, cytarabine doxorubicin/liposomal doxorubicin and 5-FU
- Onset weeks to months
- Palms and soles
- Dysesthesia and burning pain
- Sharply demarcated erythema with edematous swelling which may develop into blistering, ulceration or erosions
HAND FOOT SYNDROME

Figure courtesy of Stephanie Liu, MD
CISPLATIN + GEMCITABINE
LIPOSOMAL DOXORUBICIN

Figures: LeBoeuf
DOXORUBICIN: COOLING

CAPECITABINE HFS

Complicated by pseudomonal infection, sepsis and death

HFS, hand-foot syndrome
CAPECITABINE HFS

After 19 Months

HFS, hand-foot syndrome
Figures: LeBoeuf
HFS: MANAGEMENT STRATEGIES

• Grade 0:
  – Gentle skin care
  – [Capecitabine: Celecoxib 200mg BID]
  – [Doxorubicin: Cooling]

• Grade 1:
  – Topical high potency steroid BID
  – [Capecitabine: Celecoxib 200mg BID]
  – [Doxorubicin: Cooling]

• Grade 2:
  – Topical high potency steroid BID
  – Pain control (NSAIDs/GABA agonists)
  – [Capecitabine: Celecoxib 200mg BID]
  – [Doxorubicin: Cooling]

• Grade ≥3:
  – Hold therapy until grade 1
  – Then as above for grade 2

HAND-FOOT SKIN REACTION

- Onset between days 2 and 24 (median 15) with scaling, swelling, redness then dryness and peeling
  - Pain may be out of proportion to the appearance

- Tender hyperkeratotic lesions, with or without blisters, surrounding rim of erythema

- More pronounced on areas with increased pressure and friction

- Most common with multikinase inhibitors

INCIDENCE OF HFSR (%)

High-grade = Grade 3 (severe) according to the NCI-CTCAE (National Cancer Institute’s Common Terminology Criteria for Adverse Events) v3.0 or V4.03= ulcerative dermatitis or skin changes with pain interfering with function.

HFSR, hand-foot skin reaction

HFSR: SORAFENIB, SUNITINIB

HFSR, hand-foot skin reaction
WHAT’S BEEN TRIED?

SMALL STUDIES

• 10% Urea
• Hydrocolloid dressing containing ceramide*
• Topical heparin, shock absorbers and moisturizers
• Vitamin E 300mg/day
• Taohongsiwu (Chinese herbal)

CASES

• Clobetasol, cetirizine, cold sponging
• Topical steroids with keratolytics
• Narrow band UVB
• Topical PUVA
• Topical steroids, ‘podiatric care’ and thermal water gel
• Pregabalin
• Topical prednicarbate ointment, fusidic acid cream, dextanthenol

UVB, Ultraviolet B; PUVA, psoralen-ultraviolet A
HFSR: MY/DFCI APPROACH

• **Prior** to starting therapy
  – Skin exam and activity assessment when possible
    • Preferably involve a dermatologist
  – Treat pre-existing conditions
    • Fungal disease (athlete’s foot)
    • Dermatitis
    • Callosities
      • Pumice/friction, etc NOT recommended after starting therapy

HFSR, hand-foot skin reaction; DFCI, Dana-Farber Cancer Institute
ANTICIPATORY GUIDANCE

- Dry skin care
  - Bland moisturizers
  - Warm, not hot water
- 20% Urea cream BID
- Avoid repetitive tasks or vigorous exercise
  - Vaseline with gloves for hand oriented tasks
  - Lubricate feet like a marathoner in anticipation of activity
  - Well fitting shoes and socks
    - Cotton is ok for everyday use, but running socks* better handle moisture
- *Same story for scrotal irritation

BID, twice a day
COTTON SOCKS?

- “RULE #1 - Keep the cotton socks out of the running shoes! Why? Cotton retains moisture and when you have moisture, heat, and friction in a running shoe you are more likely to get blisters, calluses, and hot spots. Also, cotton gets more abrasive when wet, again not good in a running shoe.”

HANDS & FEET: CLINICAL PEARLS

• Dorsal hands, feet & nails:
  – Taxanes → Cooling

• Diffuse palmoplantar: HFS
  – Capecitabine → Celecoxib
  – Doxorubicin → Cooling

• Inflamed callosities: HFSR
  – Targeted therapies
  – Avoid heat and friction
  – Urea/topical steroids/retinoids

HFS, Hand-foot syndrome, HFSR, hand-foot skin reaction
Figures: LeBoeuf
LIFE THREATENING ERUPTIONS
## Life-threatening Dermatologic Adverse Events in Oncology

SJS and TEN cases from peer-reviewed literature inclusive of Ovid (1950-June 2013) and PubMed (1948-2013)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>14</td>
</tr>
<tr>
<td>Imatinib</td>
<td>9</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>7</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>5</td>
</tr>
<tr>
<td>Procarbazine, Mithramycine, Gemcitabine</td>
<td>9</td>
</tr>
<tr>
<td>Bleomycin, Pemtrexed, Cetuximab, IL-2</td>
<td>8</td>
</tr>
</tbody>
</table>
LIFE THREATENING EVENTS
FDA-ADVERSE EVENT REPORTING SYSTEM

<table>
<thead>
<tr>
<th>Drug</th>
<th>SJS Cases (N)</th>
<th>TEN Cases (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>Busulfan</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Lomustine</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Photo courtesy of Milan Anadkat.
EPIDERMAL NECROLYSIS: BORTEZOMIB

Red Flags ➔ Urgent Consult or ER:

- Blisters
- Skin Tenderness
- Rapid progression, turning dusky
- Sloughing
- Mucous Membrane Involvement

Stop all non-essential medications
Systemic therapy case by case

ER, emergency room
SUMMARY

- Cytotoxic, targeted and immunotherapy regimens may result in specific and sometimes predictable dermatologic adverse events
- Recognition of specific toxicities brings clarity when agents are combined
- Preventative strategies and reactive management can help improve patient outcomes
- Dermatologists can be key members of the cancer patient care team
People come into my office looking for unconditional love or complaining that their spouse does not offer it. Now I can tell them they already have it.

Their epidermis caresses them, contains them, bends anyway they like, and asks nothing in return. Maybe we hydrate it or protect it from the sun, but that is hardly an equal partnership.

I will never take my skin for granted again.
MANAGEMENT OF SKIN TOXICITIES IN TREATMENT OF COLORECTAL CANCER

Jeff Wiisanen, MD
Mayo Clinic, Rochester, MN

October 19th, 2019
Dr. Jeff Wiisanen does not have any relevant financial relationship to disclose.
OUTLINE

- EGFR inhibitors
  - cetuximab and panitumumab

- Chemotherapy
  - capecitabine

- Multikinase inhibitor
  - regorafenib

- Immunotherapy
EGFR INHIBITORS-INDUCED SKIN TOXICITY

- Acneiform, papulopustular rash
  - cosmetically sensitive areas (↑ sebaceous glands), causes pain and pruritus, and may impair the patient’s quality of life and adherence to cancer therapies
- Xerosis (dry), pruritus and paronychia (nail infection)
- 80% incidence
  - Men and age <70: ↑ risk of severe rash¹
- Within first 2 weeks, up to 8 weeks
- Predictive factor for survival (HR 0.51; p<0.00001) and progression (HR 0.58; p<0.00001)²
  - Patients with moderate or severe rash had an increased chance of response (35 vs 13%; RR 2.23, p<0.00001)

EGFR, epidermal growth factor receptor; HR, hazard ratio; RR, response rate

¹Jatoi A et al. Oncology 2009;77:120–123
MANAGEMENT OF EGFR INHIBITOR CUTANEOUS TOXICITY

- **Pruritus**
  - anti-histamines, aprepitant\(^1\), GABA agonists
- **Rash**\(^2\)
  - steroids (topical/systemic)
  - antibiotics (topical/systemic)
  - oral isotretinoin
- **Prevention**\(^3\)
  - tetracycline
  - significantly lower incidence grade 2-3 folliculitis
  - better quality of life

---

**Treatment of EGFR inhibitor-induced acneiform rash**

<table>
<thead>
<tr>
<th>Severity (CTCAE v.4)</th>
<th>Intervention (reactive) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Prophylactic therapy with sunscreen SPF 30+; moisturizing cream; gentle skin care instructions given</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Continue anticancer agent at current dose and monitor for change in severity. Hydrocortisone 2.5% cream and clindamycin 1% gel. Reassess after two weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue anticancer agent at current dose and monitor for change in severity. Hydrocortisone 2.5%, desonide, aclometasone 0.05% cream to the face and neck or fuscoserine 0.03% cream to check and back. AND Doxycycline 100 mg OR minocycline 100 mg bid. Reassess after two weeks (either by healthcare professional or patient self-report); if reactions worsen or do not improve proceed to next step</td>
</tr>
<tr>
<td>Grade 3 or intolerable grade 2</td>
<td>Dose modify as per PI. Obtain bacterial/viral cultures if infection is suspected and continue treatment of skin reaction with the following: Hydrocortisone 2.5%, desonide, aclometasone 0.05% cream to the face and neck or fuscoserine 0.03% cream to check and back. AND Doxycycline 100 mg OR minocycline 100 mg bid AND prednisone 0.3 mg/kg for seven days. Consider low dose isotretinoin (20 to 30 mg/day). Reassess after two weeks; if reactions worsen or do not improve, dose interruption or discontinuation per PI may be necessary</td>
</tr>
</tbody>
</table>

* It is recommended that patients treated with EGFR inhibitors begin prophylactic rash therapy with doxycycline 100 mg twice a day or minocycline 100 mg daily and a low potency topical steroid twice a day for first six weeks of therapy.


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CTCAE, common terminology criteria for adverse events; EGFR, epidermal growth factor receptor; GABA, gamma-aminobutyric acid

\(^1\)Santini, D. et al., Lancet Oncol. 2012 Oct;13(10):1020-4; \(^2\)Pinto C et al., Oncologist. 2011; 16(2): 228 – 238; \(^3\)Bachet JB. et al., Oncologist, 2012; 17(4), 555 – 568
CAPECITABINE (CHEMOTHERAPY) INDUCED SKIN TOXICITY

• Hand/foot syndrome (plantar-palmer erythrodysesthesia)
  – exact mechanism unknown
  – all grade: 56-63%, grade 3: 11-24%
  – symptoms begin 2-12 days after drug administration
  – redness, swelling, dryness, scaling, pain, itching, blisters
  – hands > feet

MANAGEMENT OF CAPECITABINE CUTANEOUS TOXICITY

• Avoid friction/trauma
  – protective gloves/socks

• Pain medications
  – NSAIDs may delay onset and ↓ incidence

• Steroid creams (clobetasol, betamethasone)
  – erythematous/painful areas

• Moisturizers

• Decrease dose or hold until improvement

NSAIDs, non steroidal anti inflammatory drugs
REGORAFENIB-INDUCED SKIN TOXICITY

• 2 types of skin reactions
  – HFSR (localized)
    • topical steroids and anesthetic/analgesic
    • occurrence of grade 2
      • reduce regorafenib dose to 120mg
      • if re-occurrence of grade 2
        • reduce regorafenib dose to 80mg
  – Rash/desquamation (generalized)
    • typically maculopapular
    • in CORRECT study\(^1\): 26% any grades – 6% grade ≥3
    • in IMBlaze370 study\(^2\): 21% any grades – 3% grade ≥3

• Consider holding regorafenib dose for at least 7 days in patients with:
  • recurrent grade 2 HFSR
  • Grade ≥3 HFSR
  • recurrent grade 2 HFSR that does not improve within 7 days of dose reduction

• Avoid alcohol-based lotions, excessive drying of the skin, skin irritants, limit sun exposure

HFSR, hand/foot skin reaction
MANAGEMENT OF REGORAFENIB CUTANEOUS TOXICITY

Patient starts on regorafenib therapy

Before symptoms develop

- Full-body examination at start of therapy
- Management of predisposing risk factors
- Prophylactic urea 10%
- Clinical review within 2 weeks of starting treatment to identify incipient symptoms and reinforce patient education

Patient education (verbal and written), with advice to:

- Avoid heat, constrictive footwear or vigorous activities that place stress on the extremities
- Moisturize liberally
- Wear thick cotton gloves and socks to prevent injury and protect the hands and feet

If grade 1 symptoms develop

(Minimal skin changes or dermatitis [e.g. erythema, edema, or hyperkeratosis] without pain)

- Keratolytics (e.g. 10–40% urea or 5–10% salicylic acid)
- Topical analgesics (e.g. lidocaine gel)
- Maintain regorafenib dose level
- Clinical review within 2 weeks

Reinforced patient education on prevention approaches:

- Avoidance of hot water
- Frequent use of emollients and creams
- Use of cotton gloves and socks

If grade 2 symptoms develop

(Skin changes [e.g. peeling, blisters, bleeding, edema, or hyperkeratosis] with pain, limiting instrumental activities of daily living)

- As for grade 1 symptoms (with topical lidocaine for pain), with addition of clobetasol 0.05% ointment for erythema
- Consider decreasing regorafenib dose; if symptoms do not improve or recur, interrupt treatment for ≥7 days until toxicity resolves

Reinforce patient education on preventive approaches

If grade 3 symptoms develop

(Severe skin changes [e.g. peeling, blisters, bleeding, edema, or hyperkeratosis] with pain, limiting self-care activities of daily living)

- As for grades 1 and 2 symptoms
- Consider adding topical antibiotics or antiseptics to clobetasol 0.05% ointment
- Interrupt treatment for ≥7 days until toxicity resolves and reintroduce regorafenib at a reduced dose

Reinforce patient education on preventive approaches
IMMUNOTHERAPY INDUCED SKIN TOXICITY

- Onset variable
  - even after cessation
- Incidence 27-71%
  - ↑ incidence with combination
  - Grade ≥ 3 (0-9.6%)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>138 (32)</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>120 (28)</td>
</tr>
<tr>
<td>Psoriasiform</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Bullous</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>21 (5)</td>
</tr>
<tr>
<td>Eczematous</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>61 (14)</td>
</tr>
</tbody>
</table>

ircAEs (n=427)

ircAEs, immune-related cutaneous adverse events
# MANAGEMENT OF IMMUNOTHERAPY INDUCED SKIN TOXICITY

<table>
<thead>
<tr>
<th>Management</th>
<th>GABA, gamma-aminobutyric acid; ICIs, immune checkpoint inhibitors; IL-6, interleukin 6; MPR, methylprednisolone; NB-UVB, narrow band ultraviolet B rays; OTC, over the counter; TNF, tumor necrosis factor Phillips GS et al. J Clin Oncol 2019 Jun 19:JCO1802141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
<td>Management</td>
</tr>
<tr>
<td>Grade 0</td>
<td>Patient counseling  Gentle skin care education  OTC emollients</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Continue ICIs at current dose and monitor for change in severity</td>
</tr>
<tr>
<td></td>
<td>Continue ICIs at current dose and monitor for change in severity</td>
</tr>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day</td>
</tr>
<tr>
<td></td>
<td>Reassess after 2 weeks either by healthcare professional or patient self-report; if reaction worsens or dose not improve, proceed to next step</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Continue ICIs at current dose and monitor for change in severity</th>
<th>Hold ICIs until grade 0-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day and oral corticosteroids (prednisolone 0.5-1 mg/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day and GABA analogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day and NB-UVB phototherapy or apremilast</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-potency topical corticosteroid twice a day and oral corticosteroids (prednisolone 0.5-1 mg/kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reassess after 2 weeks; if reaction worsens or dose not improve, proceed to next step</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade &gt; 2 or intolerable grade 3</th>
<th>Interrupt ICIs until severity decreases to grade 0-1; dose modify as per protocol and monitor for change in severity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral corticosteroids (prednisolone 0.5-1 mg/kg) or biologics (infliximab, tocilizumab)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral antihistamines and GABA analogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biologics (infliximab, pembrolizumab, adalimumab, apremilast)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral corticosteroids (prednisolone 0.5-1 mg/kg) and rituximab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reassess after 2 weeks; if reaction worsens or dose not improve, dose reduction or discontinuation per protocol may be necessary. For corticosteroid resistant MPR or NB-UVB rash, check serum levels of IL-6 and TNF-α to assess for eligibility for targeted therapy (eg, tocilizumab, infliximab)</td>
<td></td>
</tr>
</tbody>
</table>
CASE

- 62 year old female with iron-deficiency anemia

- Colonoscopy
  - Fungating mass in descending colon
  - Bx: poorly-differentiated adenocarcinoma
  - CEA: 19.4

- CT imaging
  - Liver: multiple 2-4cm masses
    - Bx: adenocarcinoma
    - KRAS/NRAS/BRAF WT, pMMR/MSI-L
  - Chest: multiple small nodules (<1cm)

- Started on FOLFOX with Panitumumab
  - Flushing and ‘acne’ after 2 cycles

- After 4 cycles

QUESTIONS

1) After a treatment break what should we do to increase the chances that the patient gets full dose therapy at each cycle whilst maintaining the best QoL?

2) Should we have done anything differently to have prevented this?

https://www.lindiskin.com/egfr-face-rash

BRAF WT, BRAF wild-type; Bx, biopsy; CEA, carcinoembryonic antigen; CT, computerized tomography; FOLFOX, folinic acid, fluorouracil and oxaliplatin; MSI-L, microsatellite instability low; pMMR, mismatch repair proficient
EFFECTIVE MANAGEMENT OF SKIN TOXICITIES IN THE TREATMENT OF METASTATIC COLORECTAL CANCER

Pritish Iyer, MD
Fox Chase Cancer Center/Temple University,
Philadelphia, PA

October 19th, 2019
DISCLOSURE

Dr. Pritish Iyer does not have any relevant financial relationship to disclose.
CHEMOTHERAPY ASSOCIATED SKIN TOXICITIES IN COLORECTAL CANCER

- Anti-EGFR (cetuximab, panitumumab)
- Anti-VEGF (bevacizumab, ramucirumab)
- Regorafenib
- Capecitabine
- Immunotherapy/Checkpoint Inhibitors
- BRAF inhibitors (dabrafenib, vemurafenib)

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor receptor
PREVENTION AND CONSERVATIVE MANAGEMENT OF SKIN TOXICITIES

• Hydration
• Moisturizing hands and feet
• UVA/UVB, SPF 15+ sunscreen applied every 2 hours, more often if sweating
• Keep nails short, clean, and use sterile tools
• Avoid irritation with nail polish removal chemicals, hair waxing, or perfumed soaps
  – Use gloves when doing dishes

UVA, ultraviolet A; UVB, ultraviolet B; SPF, sun protection factor
ANTI-EGFR THERAPY ASSOCIATED SKIN TOXICITIES

• Variable presentation:
  – Soreness, tightness, itchiness
  – Pimple-like bumps on face and neck
  – Cracks on skin and nail changes, red vessels seen on the skin

• Prevention:
  – Topical steroids (hydrocortisone 2.5%)
  – Oral antibiotics (doxycycline 100 mg BID x 6 weeks)

• Treatment
  – Similar to prevention
  – If grade 3: hold drug and consider oral steroids

EGFR, epidermal growth factor receptor
Source picture: Melosky et al., Curr Oncol 2015
References for further information: Zalcman G et al. JCO 2016; Ding PN et al. JTO 2016
PALMAR-PLANTAR ERYTHRODYSESTHESIA ASSOCIATED WITH CHEMOTHERAPY (HAND FOOT SYNDROME)

- Initially presents as tingling in hands and feet, followed by painful erythema and swelling of hands and/or feet
- Prevention: topical urea cream 10% TID
- Treatment:
  - High potency topical steroids (clobetasol, betamethasone)
  - Salicylic acid 6% or ammonium lactate 12%
  - If limiting activities of daily living (grade 2), hold drug
  - Usually resolves within 4 weeks of drug discontinuation

TID, three times daily;
Source picture: Farr et al. Case Reports in Oncology, 2011
CASE

- 36 year old female with sigmoid adenocarcinoma metastatic to liver (BRAF WT, RAS WT) who began treatment with FOLFOX + cetuximab
- After cycle 1 developed an acneiform rash over her face which was cosmetically distressing, causing her to skip every other treatment

QUESTIONS

1) After a treatment break what should we do to increase the chances that the patient gets full dose therapy at each cycle whilst maintaining the best QoL?

2) Should we have done anything differently to have prevented this?

BID, twice daily; FOLFOX, folinic acid, fluorouracil and oxaliplatin; QoL, quality of life; WT, wild-type

Source picture: Melosky et al. Curr Oncol 2015 (illustration of acneiform rash)