Cutaneous reactions to targeted therapies

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Disclosures

• I have no relevant disclosures
Papulopustular Eruption
Papulopustular Eruption

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

- More common with monoclonal antibodies than TKIs
- Most common dermatologic adverse event of EGFRIs
- Related to disruption of keratinocyte differentiation
Papulopustular Eruption

• Onset: 1-2 weeks after initiation of therapy
  • Peak intensity at 4 weeks
• Scalp, face, neck, chest, back >> abdomen, extremities
• Signs and symptoms:
  • Papules and pustules
  • Pruritus, pain, burning
# Papulopustular Eruption Grading

**Common Terminology Criteria for Adverse Events 4.0**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papules and/or pustules covering &lt;10% BSA, which may or may not be associated with symptoms of pruritus or tenderness</td>
<td>Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; <strong>limiting instrumental ADL</strong></td>
<td>Papules and/or pustules covering &gt;30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; <strong>limiting self care ADL</strong>; associated with <strong>local superinfection</strong> with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with <strong>extensive superinfection</strong> with IV antibiotics indicated; life threatening consequences</td>
<td>Death</td>
</tr>
</tbody>
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Common Terminology Criteria for Adverse Events 4.0
Papulopustular Eruption

Preventive Therapy:
• Tetracycline and low potency steroid for first 6 weeks
• Sunscreen, moisturizing creams
• Gentle skin care

Treatment:
• Grade 1: HCT 2.5% + Clindamycin 1% lotion
• Grade 2: HCT 2.5% + Doxycycline or Minocycline 100 mg BID
• Grade 3:
  • HCT 2.5% + Doxycycline or Minocycline 100 mg BID + Prednisone 0.5 mg/kg for 5 days
  • Dose modification, treatment interruption
  • Culture
• Avoid topical retinoids, benzoyl peroxide, and pimecrolimus
A 32 yo female on Erlotinib has a papulopustular eruption that is not responding to Doxycycline 100 mg BID, topical Clindamycin 1% lotion and Aclometasone. She continues to have numerous, symptomatic, papules and pustules after 4 weeks of therapy. What is the next best step?

A. Switch from Doxycycline to Minocycline
B. Add Benzoyl Peroxide
C. Use a stronger topical steroid
D. Perform a bacterial culture
Unique presentations of epidermal growth factor receptor inhibitor-induced papulopustular eruption related to bacterial superinfection
Lauren Elyse Wiznia BA, Jennifer Nam Choi MD
Dermatology Online Journal 19 (3): 8

Yale University School of Medicine, New Haven, Connecticut
Cutaneous Adverse Effects With HER1/EGFR-Targeted Agents: Is There a Silver Lining?

Román Pérez-Soler and Leonard Saltz
Erlotinib: Rash and Survival

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of Patients</th>
<th>Median (95% CI) days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44</td>
<td>103 (64 to 140)</td>
</tr>
<tr>
<td>1</td>
<td>67</td>
<td>191 (145 to 260)</td>
</tr>
<tr>
<td>2/3</td>
<td>95</td>
<td>266 (227 to 319)</td>
</tr>
</tbody>
</table>

\[ P (0 \text{ v } 1) = .0001 \]
\[ P (0 \text{ v } 2/3) = .0001 \]
\[ P (1 \text{ v } 2/3) = .20 \]
Cetuximab: Rash severity and survival

Gefitinib: Rash and Survival

\[ P = .0835 \]

Event-Free Probability

- Rash toxicity absent (n = 20)
- Rash toxicity present (n = 32)

Time (weeks)

Question 3

What topical agent would you want to avoid in treating a papulopustular eruption secondary to Cetuximab?

A. Minocycline
B. Tretinoin 0.05%
C. Hydrocortisone 2.5%
D. Clindamycin 1% lotion
Paronychia and Other Nail Findings
Nail Findings

• Paronychia
• Pyogenic Granuloma Like Lesions
• Ingrown Nails
• Subungual Hemorrhages (Sorafenib)
• Brittle Nails
Paronychia

• EGFR inhibitors
• Multikinase inhibitors
• MEK inhibitors
• BRAF inhibitors
• HER2 inhibitors
• CTLA4 inhibitors
• PD-1 inhibitors
• mTOR inhibitors
• RET inhibitors

• Onset: 1-6 months after initiation
• Affects 10-15% of patients
• Great toe and thumbs most commonly affected
• Can persist for months despite treatment interruption
• Secondary infection – S. Aureus, Candida, Pseudomonas
Paronychia Treatment

**Prevention**
- Comfortable shoes with wide toe box
- Podiatry to treat any hyperkeratotic skin

**Treatment**
- Vinegar soaks (1:1 for 15 minutes daily)
- Topical antibiotics
- Warm compresses
- Potent Topical steroids
- Silver nitrate
- Oral antibiotics
- Culture if suspect infection
Hand Foot Skin Reaction
Hand Foot Skin Reaction

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors
Hand Foot Skin Reaction

• Most likely cutaneous toxicity to result in treatment interruption
• Onset: first 2-4 weeks of therapy
• Signs and symptoms:
  • Pressure and friction areas
  • Fingertips, heels, over joints, interdigital web spaces, lateral feet
  • Increased Hyperkeratosis
  • Erythema, desquamation, bullous lesions
  • Erythematous halo
  • Bilateral and symmetric
  • Soles > palms
  • Paresthesia, burning, pain, heat intolerance
• Pathogenesis: VEGF and PDGF inhibition affect on vessel repair and vessel regression
Hand Foot Skin Reaction

**Prevention**
- Podiatry Evaluation
- Orthotist evaluation
- Roomy footwear
- Wear thick socks and gloves
- Avoid pressure or friction
- Avoid excessive temperatures
- Exam prior to starting – assess for malalignment, hyperkeratosis, eczema
- Mild soaps

**Treatment**
- Grade 1
  - Liberal moisturizers
  - Thick socks and gloves at night
- Grade 2 & 3
  - Topical antibiotics to blisters and erosions
  - Topical steroids Class 1 BID to erythematous/inflamed areas
  - Topical Keratolytics BID to hyperkeratotic areas
    - Salicylic acid 6%
    - Urea 20 to 40%
    - Tazarotene
  - Pain Management
  - Dose interruption x 1 week

Patricia Gomez, and Mario E. Lacouture The Oncologist 2011;16:1508-1519
Question 4

Podiatry consultation in a patient receiving targeted therapy can prevent:

A. Cracks and Fissures of the palms and soles
B. Hand Foot Skin Reaction
C. Hand Foot Syndrome
D. Paronychia
Increased Neoplasms
Neoplasms

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- RET inhibitors

- Actinic Keratoses
  - BRAFI
- Squamous Cell Carcinomas
  - BRAFI
- Melanocytic Proliferations
  - Multikinase Inhibitors, BRAFI
- Seborrheic keratoses
  - BRAFI
- Verruca Vulgaris
  - BRAFI
Atypical squamous cell proliferations

• 10% of patients taking Sorafenib
• Keratoacanthomas
• Invasive SCC

• Treatment:
  • Excision
  • Oral retinoids
  • Electrodesiccation & Curettage (ED&C)
  • Close monitoring
BRAF Inhibitors

Keratinocytic

- Verrucal Keratoses & Warts
  - Cryotherapy
  - PDT
  - ED&C
  - 5-fluorouracil
  - Imiquimod
  - Keratolytics
  - Low threshold to biopsy

- Keratoacanthomas and SCC
  - ED&C
  - Surgical excision
  - PDT
  - Systemic retinoids
  - IL 5-fluorouracil

Melanocytic

- Dynamic changes in existing nevi
- Eruptive Nevi
- Melanoma

- Close monitoring every 4 to 6 weeks
- Low threshold to biopsy
- Sun protection
Question 5

• The combination of BRAF inhibitors and __ Inhibitors may reduce the cutaneous adverse events of both classes of drugs:

• MEK
• EGFR
• HER2
• mTOR
• BCR-ABL
Phototoxicity
Phototoxicity

• Increased risk of photosensitivity
  • Photoallergic and phototoxic reactions
  • Hyperpigmentation

• EGFRI cutaneous adverse events may be augmented by UV radiation

• Prevention:
  • Broad spectrum sun block
  • Avoidance of Sun
  • Avoid photosensitizing medications

• EGFR inhibitors
• Multikinase inhibitors
• MEK inhibitors
• BRAF inhibitors
• HER2 inhibitors
• CTLA4 inhibitors
• PD-1 inhibitors
• mTOR inhibitors
• RET inhibitors
CASE REPORT

Photoallergic reaction in a patient receiving vandetanib for metastatic follicular thyroid carcinoma: a case report

Jennifer Goldstein¹, Anisha B. Patel², Jonathan L. Curry³, Vivek Subbiah⁴ and Sarina Pha-Paul⁵
Hair Changes
Hair Changes

• Hypertrichosis
• Scalp Alopecia
• Trichomegaly
Scalp Alopecia

- EGFR inhibitors
- Multikinase inhibitors
- MEK inhibitors
- BRAF inhibitors
- HER2 inhibitors
- CTLA4 inhibitors
- PD-1 inhibitors
- mTOR inhibitors
- Hedgehog Pathway Inhibitors
- RET inhibitors
Dyspigmentation
Dyspigmentation

• Hypopigmentation – c-kit inhibition
• Hyperpigmentation
• Yellowing

• EGFR inhibitors
• Multikinase inhibitors
• MEK inhibitors
• BRAF inhibitors
• HER2 inhibitors
• CTLA4 inhibitors
• PD-1 inhibitors
• mTOR inhibitors
• RET inhibitors
Unique Cutaneous Reaction to Second- and Third-Generation Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia

Anisha B. Patel, Alvin R. Solomon, Michael J. Mauro, Benjamin D. Ehst

• Keratosis Pilaris - like eruption
• Lichen Planopilaris – like eruption
• Scarring and non-scarring hair loss

EGFR inhibitors
Multikinase inhibitors
MEK inhibitors
BRAF inhibitors
HER2 inhibitors
CTLA4 inhibitors
PD-1 inhibitors
mTOR inhibitors
RET inhibitors
A 45 yo male with a gastrointestinal stromal tumor is undergoing therapy with a new agent. He notes yellow discoloration of his skin. On exam the discoloration is not noted in his mouth and his eyes are nonicteric. What medication is the culprit?

A. Methotrexate  
B. Pembrolizumab  
C. Sunitinib  
D. Dasatinib  
E. Vemurafenib