Coping With Confidence: Tips and Techniques for Managing Treatment-Induced Rash

Saturday, May 3, 2014
Anaheim Marriott • Anaheim, CA
Overview and Incidence of Therapy-Induced Rash
Addressing Dermatologic Events in Cancer Patients...Are we being too superficial?

- 1.6 million people with cancer in US
  - Prior to therapy, 45.1% with skin findings (n=700)
  - Tinea pedis/onychomycosis, xerosis, pruritus, pyoderma
  - 900,000 receive chemotherapy
  - 700,000 receive radiotherapy
  - Most will have a surgical procedure

- Consequences of dermatologic conditions in cancer
  - Psychosocial impact
  - Financial burden
  - Physical health
  - Anticancer treatment disruption

Guillot et al, 2004; Wang et al, 2007; Kilic et al, 2007; Ghandi et al, 2009; Cunningham et al, 2010
You are Targeting Cancer...

Pertuzumab

*Cetuximab, *Trastuzumab

Erlotinib, Gefitinib

*Lapatinib

*Everolimus

Pyrimidines/Tubulin/Topoisomerase II
Or Targeting The Skin?

- HER2
- PI3K/Akt
- mTOR
- Tubulin
- Pyrimidine
- EGFR
- Topoisomerase II
- PDGFR/VEGFR
Dermatologic AEs of Top-Selling Agents

- Top drugs for 2007 by sales
- Percent of patients with dermatologic toxicities
- Combined sales US$15 billion Q1-2 in 2007

Sales figures from reports to the Security and Exchange Commission (SEC); drug Pis 2008; drugs.com/top200;
Dermatologic AEs of Oncology Agents

- Selected top agents used in oncology
- Percent of patients with dermatologic toxicities
- Combined sales US$4.8 billion Q1-2 in 2008

C-mab, Erlotinib, Lapatinib, Capecitabine, Gemcitabine, Docetaxel, Peg-Dox, Sorafenib, Irinotecan

Sales figures from reports to the Security and Exchange Commission (SEC); drug PIs 2008
Descriptive terminology which can be utilized for Adverse Event (AE) reporting.

An AE is any unfavorable and unintended sign symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

CTCAE is mandatory in oncology trials

Gradation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>
Treatment of EGFR Antagonist-Induced Skin Rash: Results of a Survey Among German Oncologists

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td>Private practice</td>
<td>29</td>
<td>(20)</td>
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<tr>
<td>Hospital</td>
<td>120</td>
<td>(80)</td>
</tr>
<tr>
<td>Male</td>
<td>97</td>
<td>(65)</td>
</tr>
<tr>
<td>Female</td>
<td>52</td>
<td>(35)</td>
</tr>
<tr>
<td>Medical oncology</td>
<td>106</td>
<td>(71)</td>
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<tr>
<td>Dermatologic oncology</td>
<td>43</td>
<td>(29)</td>
</tr>
<tr>
<td>Age *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>24</td>
<td>(16)</td>
</tr>
<tr>
<td>35–44</td>
<td>61</td>
<td>(41)</td>
</tr>
<tr>
<td>45–54</td>
<td>50</td>
<td>(34)</td>
</tr>
<tr>
<td>55–64</td>
<td>12</td>
<td>(8 )</td>
</tr>
<tr>
<td>65+</td>
<td>1</td>
<td>(1 )</td>
</tr>
</tbody>
</table>

*1 oncologist not indicating age.
# Treatment of EGFR Antagonist-Induced Skin Rash: Results of a Survey Among German Oncologists

<table>
<thead>
<tr>
<th>Grade</th>
<th>All (n = 149)</th>
<th>MO (n = 106)</th>
<th>DO (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MO = Medical oncologist; DO = dermatoncologist.

### Local treatment, n

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All (n = 149)</th>
<th>MO (n = 106)</th>
<th>DO (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>135 (91%)</td>
<td>55</td>
<td>11</td>
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<tr>
<td>Metronidazole</td>
<td>27</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>40</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>Nadifloxacin</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>4</td>
<td>3</td>
<td>1</td>
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</table>

### Systemic treatment, n

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All (n = 149)</th>
<th>MO (n = 106)</th>
<th>DO (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>50</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Minocycline</td>
<td>47</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Dose reduction, %</td>
<td>3.5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Delay of treatment, %</td>
<td>12</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

MO = Medical oncologist; DO = dermatoncologist.
What caused these reactions?
What caused these reactions?
What caused these reactions?
Dermatologic Evaluation of Cancer Patients

- Referral to dermatology 8%
- Establishment of referral system critical
- Appointment wait times
  - Changing nevi: 38 days (n=851)
  - Botox: 8 days (n=455)

Tsang et al, JAAD 2006; Resneck et al, JAAD 2007; Boone et al, Oncology 2007
Acneiform Rash: EGFR inhibitors

- Pruritus and tenderness in 62%

- Lapatinib
  - Single agent: 55%
  - +paclitaxel: 74%
  - +nab paclitaxel: 67%

- Pertuzumab
  - All grade: 25%
  - Grade 3: 1%

- Erlotinib
  - All grade: 75%
  - Grade 3: 9%

- Cetuximab
  - All grade: 85%
  - Grade 3: 10%

Acneiform Rash: EGFR inhibitors

- Pruritus and tenderness in 62%
- Lapatinib
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  - All grade: 85%
  - Grade 3: 10%

Effect Of Chemotherapy On High-grade Acneiform Rash

- 9 trials
- 5,533 patients
  - 2,664 C+Ch

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (95% CI)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab in combination with chemotherapy</td>
<td>73.1 (68.9–77.0)</td>
<td>11.4 (7.4–17.6)</td>
</tr>
<tr>
<td>High grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab in combination with chemotherapy</td>
<td>12.8 (9.1–17.7)</td>
<td>37.7 (17.8–80.0)</td>
</tr>
<tr>
<td>Cetuximab monotherapy</td>
<td>6.3 (3.7–10.5)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Relative risk:
- All grade: 11.4 (95% CI 7.4–17.6, P<0.001)
- Hi grade: 2.03 (95% CI 1.52–2.71, P<0.01).
Acneiform Rash: Taxanes

- Incidence: 1-13%; Pruritus in most
- Treat with topical steroids/antibiotics
Adverse Events to Systemic Therapy: Xerosis

- Survey of survivors (n=379)
  - Xerosis in 34%
  - Negative impact on QoL in 44%

- Complications
  - Pruritus
  - Secondary infections
  - Fissures

**Pruritus**

- Patients treated with targeted therapies

- Pruritus (n=17,375)
  - Ipilimumab: 31%
  - EGFR inhibitors: 18-54%
  - Afatinib: 16%

- Decreased QoL

- Associated with pain/infections

- Increased mast cells in pruritus unassociated with lesions

Adverse Events to EGFRIs/mTORIs: Paronychia

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-grade</td>
<td></td>
</tr>
<tr>
<td>EGFR inhibitors</td>
<td>17.2 (13.8-21.3)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>14.9 (11.9-18.5)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>16.3 (12.4-21.1)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>25.6 (15.5-39.2)</td>
</tr>
<tr>
<td>Lapatinib*</td>
<td>N/A</td>
</tr>
<tr>
<td>High-grade</td>
<td></td>
</tr>
<tr>
<td>EGFR inhibitors</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>1.0 (0.4-2.3)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>1.8 (0.8-3.8)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>1.4 (0.7-2.8)</td>
</tr>
<tr>
<td>Lapatinib*</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dermatologic Infections Complicating Rash

- Staphylococcus aureus
  - Carrier rates of 11%-32%
    - CA-MSSA SSTI (85-95%):
    - MRSA in up to 38%

- In oncology SSTI may result in bacteremia
  - Skin and mucosa entry in 64%
  - 16% mortality

- An analysis of 221 patients treated with EGFRIs was conducted
  - 38% with bacterial, viral, fungal
  - Higher risk in leukopenic patients (p<0.05)

Coping With Confidence: Tips and Techniques for Managing Treatment-Induced Rash

Eilers et al, JNCI 2010.
Impact of Rash on QoL and Cost

Quality of Life
- Survey of 58 patients w/Skindex 16
- Top domain: Emotions (p<0.05)
- Inverse corr age-emotions (r=-0.26, p =0.03)

Cost
- Median cost/pt: $2715

Survey: Rash, Paronychia, Xerosis, Pruritus, Alopecia

NCI-CTCAE v3.0 HFSR Grade

Skindex Score

Joshi et al, Cancer 2010; Borovicka et al, Arch Derm 2012
Correlation: Acneiform Rash and Response

**Median Overall Survival**

- Vincenzi 2006: HR, 0.72; 95% CI, 0.54-0.97
- Saltz 2004: p=0.02
- Hecht 2007: G 0, G 2-3

**Dose Modifications**

**Oncology HCP Surveyed**

- Discontinue
- Dose Modify

**Rash**

- G 0-2: cetuximab
- G 3: cetuximab
- G 0: panitumumab
- G 1: panitumumab

**Months**

- 0, 5, 10

**Percent**

- 0, 20, 40, 60, 80, 100

Boone et al, *Oncology* 2007
Maculopapular Rash

- Common presentation
  - Liposomal doxorubicin: 18%
  - Lapatinib + paclitaxel: 74%
  - NSAIDs, antibiotics
- Associated with pruritus/pain
- Dose modification or d/c frequent
- Treatments
  - Oral Antihistamines
  - Steroids
    - Grade 1 (topical)
    - Grade 2/3 (topical/oral)

Maculopapular/Acneiform Rash: mTOR inhibitors

- Clinical/histology (n=11)
  - Papulopustular in 7
  - Maculopapular in 4
  - Varied histology

- Rash incidence and risk (n=2,242)
  - Incidence 28.6%
  - Highest incidence: BC
  - High grade 1%
Rash to Gemcitabine

• Peripheral edema
  – All grade: 20%
  – Grade 3: 1%
  – Treatment
    • Dexamethasone
    • Stockings
    • Anti-h1

• Erysypeloid reaction
  - No findings consistent w infection
  - Anecdotal reports
  - No improvement with antibiotics

Adverse Events to Ipilimumab

- After the 2nd cycle
- Rash
  - All grade: 19%
- Pruritus
  - All grade: 4%
- Dose modification or d/c frequent
- Treatments
  - Oral Antihistamines
  - Steroids
    - Grade 1 (topical)
    - Grade 2/3 (topical/oral)

Minkis et al, JAAD 2013; Photo courtesy of Prof A Hauschild
Hand Foot Syndrome (HFS) to Cytotoxic Chemotherapy

- Associated with
  - Pain
  - Infections

- Occurs in 6-42%
  - Fluorouracil
  - Capecitabine
  - Doxorubicin

- Treatment
  - Pyridoxine (Vit B6) NOT effective
  - Liposomal doxorubicin (Dexamethasone 8mg bid for 5 days)

Getting a Grip on Hand Foot Syndrome

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Taxanes</th>
<th>Anthracyclines/Antimetabolites</th>
<th>Multikinase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion type</td>
<td>Erythematous maculopapules</td>
<td>Edema, erythema and, fissuring</td>
<td>Blisters with erythematous halo, followed by hyperkeratosis</td>
</tr>
<tr>
<td>Schedule specific</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Location in hands</td>
<td>Dorsal</td>
<td>Ventral, diffuse palmar</td>
<td>Ventral, digit tips, over IP joints, thenar and hypothenar</td>
</tr>
<tr>
<td>Location in feet</td>
<td>Dorsal: Achilles tendon, malleoli</td>
<td>Ventral: diffuse soles</td>
<td>Ventral: heels, forefoot</td>
</tr>
<tr>
<td>Nail changes</td>
<td>Onycholysis</td>
<td>Hyperkeratosis</td>
<td>Subungual hemorrhages</td>
</tr>
</tbody>
</table>
Does Development of HFS From Capecitabine Indicate Better Outcomes?

Alopecia to Targeted Therapies

- Grade 1 alopecia
- After 3 months of therapy
- Associated with curling
- Incidence
  - Erlotinib: 5-10%
  - Cetuximab: 40%
  - Sorafenib: 30%
  - Vemurafenib: 20%
Alopecia to Endocrine Therapies

• Frequently underreported (94%)
• Androgenetic type
• After 28 weeks
• Decreased diameter in frontal
• Meta-analysis of phase II-III trials
  – Patients: 13,415 (35 trials)
  – Incidence: 12% (95% CI: 11.0%–13.3%)
  – Highest with tamoxifen
  – RR 12.957 (95% CI: 7.51–22.37, p<0.01)
Persistent Alopecia

- **Chemotherapy or RT**
  - Incidence unknown
  - Busulfan+SCT (29%)
  - CTC (30%)
  - Paclitaxel, docetaxel (n=5)

- **CCSS (14,358 survivors)**
  - Persistent hair loss 14%

- **Higher risk of depression**
  - (RR 1.38; 95% CI 1.12-1.70)

- **Higher risk of anxiety**
  - (RR 1.42; 95% CI 1.18-1.71).

Hirsutism and Hypertrichosis to EGFRIs

- Patients on therapy >3 months
  - Scalp alopecia and hair curling
  - Hirsutism on face
  - Eyelash trichomegaly

Photosensitivity

• Risk in BC patients
  • Cytotoxic agents
  • EGFR inhibitors
  • Areas of RT
  • Diuretics, antibiotics

• UVA (aging, spots, photosensitivity)
• UVB (skin cancer, sunburns)

• Most sunscreens/glass protect UVB
  • Zinc, titanium: UVA/UVB
SCC and KA to RAF Inhibitors: Sorafenib, Vemurafenib, Dabrafenib

• NMSC the most common human cancer

• Incidence:
  – Sorafenib 11%
  – Vemurafenib 21%

• Time to development
  – Median 6.5 mos
  – Range 0.9-43 mos

• Treatment
  – Surgical or destructive
  – No reports of metastasis
  – Dose mod infrequent

Increased Dermatologic Toxicity with Radiotherapy

- Radiation dermatitis
  - Breast cancer
  - HNSCC
  - Anogenital cancers

- Dermatitis with pain and pruritus
- Secondary infections in 23%

- Positive studies on prevention
  - Steroids (mometasone)
  - Silver sulfadiazine

Late Effects from Cancer Treatment

- Psychosocial impact
- Functional effects

What caused these reactions?

Sorafenib HFSR

Roger Federer-Tennis calluses
What caused these reactions?

Erlotinib acneiform rash

Kim Kardashian-Acne
What caused these reactions?

EGFR Inhibitor Trichomegaly

J Lo False Eyelashes
Skin Care Guide
for
People Living With Cancer

Mario E. Lacouture, MD
Associate Member
Memorial Sloan-Kettering Cancer Center

Coping With Confidence:
Tips and Techniques for Managing
Treatment-Induced Rash

Provided by:
IPER
Rutgers
Conclusions

• Dermatologic care is critical in oncology patients

• Early/proactive approach towards AE is advisable

• Dermatologic conditions in oncology will increase in importance
  – Adjuvant setting
  – Dose escalation and combination studies
  – Longer survival and emphasis on QoL
Thank you

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