New and Emerging Drug Reactions

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Dermatology Branch
Center for Cancer Research

Disclosures

• None
New and Emerging Drug Reactions

“There are some remedies worse than the disease”

Publilius Syrus (c.42 BC)

Cutaneous Drug Reactions

• Most common side effect of medications
  – 30% of all ADR
  – 2.25 million pts./year in US
  – 1-3% of hospitalized patients
Cutaneous adverse event diagnosis

• Dermatologist (Allergist?) as psychic
  – Polypharmacy
  – Murky drug exposure history
  – Inaccurate drug ‘allergy’ history
  – Skin biopsy “to identify offending agent”

Is the eruption a drug reaction?

• Known reaction to the drug in question?
• Previous exposure to drug?
• Exclude other causes (e.g. viral exanthem)?
• Temporal relationship between drug use and reaction?
• Improvement following drug cessation?
• Reactivation upon drug re-challenge?
Cutaneous adverse event diagnosis

- Dermatologist (Allergist?) as psychic
  - Polypharmacy
  - Murky drug exposure history
  - Inaccurate drug ‘allergy’ history
  - Skin biopsy “to identify offending agent”

- References
  - ePocrates
  - Litt’s Drug Eruption & Reaction Manual
  - www.pubmed.gov

Naranjo criteria

Table 2: The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event occur after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total: 0: doubtful 1-4: possible 5-8: probable 9 or >: definite
Case 1

• Iatrogenic vs. innate?

40 year old with palmo-plantar psoriasis
1 month after starting adalimumab: Is this eruption a drug reaction?

- Generalized pustular psoriasis following treatment with adalimumab for palmo-plantar disease
Anti-TNF “Paradoxical” Autoimmunity

**Table 2:** The Naranjo adverse drug reaction probability scale; To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score

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<td>0</td>
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</tr>
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<td>-1</td>
<td>0</td>
<td>2</td>
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<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Scoring:**
- 0: doubtful
- 1-4: possible
- 5-8: probable
- 9 or >: definite
The challenge(s) of cutaneous drug reactions in 2016

- Not typical ‘immunologic’ (Type I-IV) hypersensitivity reactions

- **Targeted** therapies: very specific pathways/mechanisms involved → poorly understood reactions (paradoxical)

- Anti-neoplastic reactions: long-term AE management

- ‘Class effect’ with targeted agents: Anti-TNF, EGFRi
Raf-associated follicular hyperkeratosis

Vemurafenib (BRAF inh.)

Sorafenib (Multikinase RAF inh.)

Imatinib and cabozantinib: pigment dilution

Imatinib: bcr-abl, c-kit, PDGFR

Cabozantinib: C-MET, RET, VEGFR, AXL, TKR A/B, c-kit

Vitiligo before and during imatinib Tx


During treatment

3 weeks after discontinuing drug
Case 2

- Sunburn vs. GVHD in a child

Patient 1: 15 year old boy

- Age 6:
  - Metastatic rhabdomyosarcoma

- Age 12: nonmyeloablative PBSCT
  - Day 8: acute skin GVHD
  - Day 100: lichen planus-like cGVHD
  - 20 months: vitiligo-like depigmentation
Patient 1: 15 year old boy

- Age 6: metastatic alveolar rhabdomyosarcoma

- Age 12: nonmyeloablative PBSCT
  - Day 8: acute skin GVHD
  - Day 100: lichen planus-like cGVHD
  - 20 months: vitiligo-like depigmentation
  - 34 months: intense erythema of forehead, malar cheeks, upper extremities and feet
  - Returns to NIH for presumed flare of cGVHD
Voriconazole-induced phototoxicity

- Voriconazole 200mg QD two weeks prior to onset for presumed pulmonary aspergillosis
- Dx: phototoxicity/pseudoporphyria cutanea tarda
- Tx: voriconazole replaced with posaconazole
  - Strict photoprotection instituted
  - F/u 3 weeks later: resolution of bulle/erythema improved
Voriconazole (Vfend®)

• 2nd generation orally bioavailable triazole
• FDA approval 2001
  – Invasive aspergillosis
  – Candidemia, esophageal and disseminated candidiasis

• Side effect profile
  – Vision changes (20%)
  – Hallucinations (15%)
  – Hepatic enzyme abnormalities (12-20%)
  – “Skin reactions” (attributable to drug: 7%)
    • Photosensitive rash (2%)

Brief communication

Voriconazole-induced pseudoporphyria

J P Tolland¹, P P McKeown², J R Corbett³

¹Departments of Dermatology, Belfast City Hospital Trust, Royal Hospitals Trust Belfast, ²Department of Cardiology, Royal Hospitals Trust Belfast, and ³Department of Dermatology, Royal Hospitals Trust Belfast

Fig. 1. Bullae and erosions on the dorsal aspects of the feet.

Fig. 2. Erosive lesions on lips.
**Fig. 1.** Bullae and erosions on the dorsal aspects of the feet.

**Fig. 2.** Erosive lesions on lips.

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**Voriconazole-Induced Phototoxicity Masquerading as Chronic Graft-versus-Host Disease of the Skin in Allogeneic Hematopoietic Cell Transplant Recipients**


Systemic fungal infections pose a significant risk to patients following allogeneic hematopoietic cell transplantation (alloHCT). Voriconazole (Vfend®, Pfizer) is an oral second-generation triazole antifungal agent that offers a broad spectrum of coverage against fungal species and is frequently utilized in the post-HCT setting. Herein, we describe 5 patients who were initially believed to be experiencing a flare of cutaneous chronic graft-versus-host disease (cGVHD), but who were actually exhibiting phototoxicity caused by voriconazole. A high index of suspicion for this adverse reaction in the post-alloHCT setting will prevent misdiagnosis and avoid inappropriate therapy for cGVHD.

* Biol Blood Marrow Transplant 1-7 (2008) © 2008 American Society for Blood and Marrow Transplantation

**KEY WORDS:** Graft-versus-host disease, Voriconazole, Phototoxicity, Fungal infection
Photoaging and phototoxicity from long-term voriconazole treatment in a 15-year-old girl

Fig 1. Numerous solar lentigines and epiderides on face 4 weeks after discontinuation of voriconazole treatment.

Fig 2. Solar elastosis and lentigines on back of left hand immediately after discontinuation of voriconazole treatment.
Voriconazole phototoxicity/photoaging in an AA-male with coccidiomycosis


What is the true incidence of voriconazole-induced phototoxicity?

• Product labeling not generalizable to current Tx population

• Phototoxicity requires both drug and sufficient UV exposure
  – FDA trial data: critically ill inpts ➔ limited outdoor exposure
  – NIH population: ambulatory outpt. population with chronic immunodeficiency (CGD, Job syndrome, cGVHD)

• The incidence of voriconazole-associated phototoxicity in the ambulatory (UV-exposed) population likely higher than described in product label
High frequency of voriconazole-related phototoxicity in patients with cystic fibrosis

Table 1: Description of the whole population exposed to voriconazole and comparison regarding photosensitivity groups.

<table>
<thead>
<tr>
<th>Subjects n</th>
<th>782-4</th>
<th>782-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age yrs</td>
<td>13.5 (4-30)</td>
<td>13.5 (4-26.1)</td>
</tr>
<tr>
<td>Age &lt;18 yrs</td>
<td>18 (98.5)</td>
<td>13 (98.7)</td>
</tr>
<tr>
<td>Sex male/female</td>
<td>15/7</td>
<td>6/6</td>
</tr>
<tr>
<td>Weight kg</td>
<td>44 (10.6-77)</td>
<td>41 (10.6-77)</td>
</tr>
<tr>
<td>CFTR mutation (c.908G&gt;A)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Delta</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CFTR mutation (class II)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Class IIb</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Obstructive insufficiency</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Daily dose of voriconazole</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mg</td>
<td>400 (120-400)</td>
<td>400 (120-400)</td>
</tr>
<tr>
<td>mg kg^-1</td>
<td>3.8 (2.5-34.2)</td>
<td>3.8 (2.5-34.2)</td>
</tr>
<tr>
<td>Time of drug exposure months</td>
<td>6.5 (1.3-19)</td>
<td>6.5 (1.3-19)</td>
</tr>
<tr>
<td>Treatment interruption in relation to skin reactions</td>
<td>11 (35.5)</td>
<td>11 (35.5)</td>
</tr>
</tbody>
</table>


Voriconazole-associated phototoxicity/SCC

22 yo HIV+ pt. with Bowens disease (SCC in situ) on chronic voriconazole
9 yo with cGVHD with 2 SCC on chronic voriconazole

Voriconazole and SCC

- 51 SCC/8 immunocompromised pts with chronic voriconazole-associated phototoxicity (age 9-54 yrs)

- Duration of immunosuppression
  - Median 51 mos (range 13-122 mos)

- Duration of voriconazole Tx
  - Median 46.5 mos (range 13-60 mos)

- “High-risk” immunocompr. Population
  - Correlation vs. causation

Retrospective case: control study (2003-08)
- SCC 3.1% (17/543)
- Median f/u: 36 mo; median time to SCC: 19.1 months
- 94% sun exposed surfaces

Multivariate analysis
- Duration of voriconazole: HR 2.1 (p = 0.04)
- High sun exposure residence: HR 3.8 (p = 0.0004)

Voriconazole (VFEND®) product labeling

“If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VFEND® should be discontinued.”
Case 3

- Immunobullous disease from anti-neoplastic therapy

Skin Reactions from New Anti-Cancer Therapies

- Classes
  - CTLA-4, PD-1/L1 inhibitors
  - EGFR inhibitors
  - Multikinase inhibitors
  - VEGFR inhibitors
  - BRAF inhibitors
  - MEK inhibitors

- Dermato-oncology ‘supportive care’
Case 3

- 51 year old male metastatic pancreatic CA
- Localized small pruritic papules/plaques (PD-L1/anti-TGFb)
- Skin bx: lichenoid dermatitis
- Dx: Drug-induced rash secondary to anti-PD-L1
- Resolution with topical steroids
Case 3

Drug-induced immunobullous disease

• Histology: dermal-epidermal separation with numerous eosinophils
• Consistent with bullous pemphigoid
Drug-induced immunobullous disease

- NOT drug eruption with bullae (erythema multiforme, SJS/TEN, bullous fixed drug eruption)

Erythema multiforme
Toxic epidermal necrolysis

Bullous fixed drug eruption: pseudoephedrine in Tylenol Sinus Allergy
Drug-induced immunobullous disease

- NOT drug eruption with bullae (erythema multiforme, SJS/TEN, bullous fixed drug eruption)

- Drug-induced bullous pemphigoid
  - Furosemide, PCN, sulfasalazine

- Drug-induced pemphigus vulgaris (thiol moiety)
  - Penicillamine, ACE inhibitors, gold

- Drug-induced linear IgA disease
  - Vancomycin

- DDx: Paraneoplastic pemphigus
  - Painful, progressive stomatitis

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Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): a multicentre, open-label, phase 1b trial

Krit Man*, Hyun Chul Chung, Yung Shin Kim, Rudi Geva, Daniela Cattaneo, Shijie Guo, Joseph Paul Eder, Taka Golish, Dong T. Ie, Baburam Butshili, Assunção Monte, Chiu-Chi Lin, Kenneth Pathanapong, Jared Luncford, Kenneth Emanuelsson, Jonathan Jose, Minoru Kishij, Yong Jie Bing

Summary

Background: Expression of PD-L1 has been shown to be upregulated in some patients with gastric cancer. As part of the phase 1b KEYNOTE-012 study, we aimed to assess the safety and activity of the anti-PD-1 antibody pembrolizumab in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Methods: This was a multicentre, open-label, phase 1b trial done at 13 cancer research centres in the USA, Israel, Japan, South Korea, and Taiwan. We enrolled patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. Patients received intravenous pembrolizumab at 10 mg/kg once every 2 weeks for 24 months or until progression or unacceptable toxic effects occurred. Response was assessed every 8 weeks in accordance with Response Evaluation Criteria in Solid Tumors version 1.1. The primary objectives were safety in patients who received at least one dose of pembrolizumab and the proportion of patients achieving overall responses in patients who received at least one pembrolizumab dose and who either had a post-baseline scan or who discontinued therapy because of clinical disease progression or a treatment-related adverse event before the first post-baseline scan. The study is registered with ClinicalTrials.gov, number NCT01548334, and is ongoing but no longer enrolling patients.

Findings: From Oct 23, 2013, to May 5, 2014, 39 patients were enrolled. 36 were evaluable for response by central assessment. Eight (22%, 95% CI 10–39) patients were judged to have had an overall response at central review; all responses were partial. All 39 patients were included in the safety analyses. Five (13%) patients had a total of six grade 3 or 4 treatment-related adverse events, consisting of two cases of grade 3 fatigue, one case each of grade 3 pemphigoid, grade 3 hypothyroidism, and grade 3 peripheral sensory neuropathy, and one case of grade 4 pneumonitis. No treatment-related deaths occurred.
# Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1


## Table 1. Patient demographics and diagnostic workup

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Tumor type</th>
<th>Current</th>
<th>Prior therapies</th>
<th>DIF</th>
<th>IIF</th>
<th>Time of rash onset (from start of therapy)</th>
<th>BP ELISA titers (from time taken since start of therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td>Male</td>
<td>Melanoma</td>
<td>Nivolumab</td>
<td></td>
<td>+</td>
<td>+</td>
<td>24 weeks</td>
<td>1535.5; 10.0; 1.25; 0.5; 0.25; 0.05;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ipilimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>Female</td>
<td>Melanoma</td>
<td>Durvalumab</td>
<td></td>
<td>+</td>
<td></td>
<td>17.9 weeks</td>
<td>1535.5; 10.0; 1.25; 0.5; 0.25; 0.05;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>Male</td>
<td>Non-small cell</td>
<td>Nivolumab</td>
<td></td>
<td>+</td>
<td></td>
<td>21.1 weeks</td>
<td>1535.5; 10.0; 1.25; 0.5; 0.25; 0.05;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lung cancer</td>
<td>Ipilimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DIF, direct immunofluorescence; IIF, indirect immunofluorescence; NA, not applicable (not performed).

*BP ELISA taken during steroid therapy.*
CTLA‐4 inhibitors/PD‐1, -L1 inhibitors

- **Anti-CTLA-4**: *ipilimumab* ('11, melanoma)
- **Anti-PD-1**:
  - *nivolumab* ('14, melanoma, '15 NSCLC, RCC, '16 HL)
  - *pembrolizumab* ('14 melanoma, '15 NSCLC)
- **Anti-PD-L1**: *atezolizumab* (May '16, urothelial CA)
- “Immune-mediated reactions”
  - Vitiligo, alopecia areata, dermatitis
  - Colitis, pneumonitis, hepatitis, encephalitis, uveitis, nephritis, hypophysitis
Skin Reactions from New Anti-Cancer Therapies

• Classes
  – CTLA-4, PD-1/L1 inhibitors
  – EGFR inhibitors
  – Multikinase inhibitors
  – BRAF inhibitors
  – MEK inhibitors

• Dermato-oncology ‘supportive care’

Epidermal Growth Factor Receptor Inhibitors

• Small molecule TKI
  – Gefitinib (Iressa®)
  – Erlotinib (Tarceva®)

• Monoclonal Ab
  – Cetuximab (Erbitux®)
  – Panitumumab (Vectibix™)

• EGFR/Her2
  – Lapatinib (Tykerb®)
  – Afatinib (Gilotrif®)

• Multikinase (EGFR/VEGFR/RET)
  – Vandetanib (Caprelsa®)

FDA indications: EGFR+ non-small cell lung CA, colorectal CA, head and neck CA, HER2+ breast CA, medullary thyroid CA
TABLE 1.
Dermatologic Toxicity With Anti-EGFR Therapies*

<table>
<thead>
<tr>
<th></th>
<th>Any Grade (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab^6,7</td>
<td>80-86</td>
<td>5-18</td>
</tr>
<tr>
<td>Gefitinib^8</td>
<td>62-75</td>
<td>up to 4</td>
</tr>
<tr>
<td>Erlotinib^9,10</td>
<td>75-79</td>
<td>5-10</td>
</tr>
</tbody>
</table>

Abbreviation: EGFR, epidermal growth factor receptor.
*Reported with single-agent therapy.

- Acneiform eruption
- Xerosis
- Dermatitis
- Nail abnormalities
  - Paronychia
  - PG-like lesions
  - Brittle nails
- Photosensitivity
- Telangiectasia
- Follicular abnormalities
  - Alopecia (scarring/non-scarring)
  - Trichomegaly
  - Hirsutism
  - Textural changes

EGFRi follicular abnormalities

- Onset: 2-3 months after drug initiation
- Alopecia (5-21%)
- Decreased frontal hairline growth
- Hair texture changes: fine/brittle
- Hirsutism: upper lip
- Trichomegaly
  - EGFR-mediated disruption of hair cycle (anagen → catagen)

EGFRI acneiform eruption

- Most common skin reaction
  - 43–85% of patients (Severe: 10%)
  - Cetuximab, panitumumab > erlotinib > gefitinib
  - Median onset: 7-10 days after drug initiation (> 3wks)
  - Radiation sites often spared
EGFRI eruption: natural history

- Spontaneous improvement
- Waxing and waning course
- Dose dependent (correlates with CA response)
- Cessation of therapy
  - Improvement in 1-2 weeks
  - Cetuximab: 50% persistent rash >30 days after exposure to drug
- S. aureus abscess/sepsis
**EGFRI eruption: treatment**

- Sun protection/avoidance
- Camouflage cosmetics
- Benzoyl peroxide
- Oral antihistamines
- Topical antibiotics
  - Metronidazole
  - Clindamycin
  - Erythromycin
- Systemic antibiotics
  - Doxycycline 100mg/day
- **No standardized treatment**
  - Controlled trials of interventions needed


**EGFRI rash: Therapeutic ladder**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Thick emollients/sun protection</td>
</tr>
<tr>
<td></td>
<td>Oral antihistamines</td>
</tr>
<tr>
<td></td>
<td>Topical clindamycin</td>
</tr>
<tr>
<td></td>
<td>Topical hydrocortisone 1%-2.5%</td>
</tr>
<tr>
<td></td>
<td>Topical pimecrolimus 1% cream</td>
</tr>
<tr>
<td>II/III</td>
<td>Doxycycline 100mg BID</td>
</tr>
<tr>
<td></td>
<td>Minocycline 100mg BID</td>
</tr>
<tr>
<td>III/IV</td>
<td>Delay EGFRI infusion interval (EGFRI antibodies)</td>
</tr>
<tr>
<td></td>
<td>Reduce dose of EGFRI</td>
</tr>
<tr>
<td></td>
<td>Systemic steroids (short course)?</td>
</tr>
</tbody>
</table>

Skin reactions to VEGF inhibitors

- **Selective**
  - Bevacizumab
  - Ranibizumab

- **Non-selective (MKI)**
  - Sorafenib
  - Sunitinib
  - Axitinib
  - Cabozantinib
  - Pazopanib
  - Cediranib
  - Vandetanib

Non-selective VEGF inhibitors

- **Non-selective (MKI)**
  - Sunitinib
  - Sorafenib
  - Vandetanib
  - Cabozantinib
  - Axitinib
  - Pazopanib
  - Cediranib

Support Care Cancer 2015;23:1827.
Sunitinib maleate (SU11248/Sutent®)

• Multi-kinase inhibitor
  – VEGFR1, 2, 3, PDGFR, c-KIT, FLT3, CSF-1R, RET

• Dermatologic adverse reactions
  – Rash 38%
  – Yellow pigmentation 33%
  – Hair depigmentation 17%
  – Hand-foot syndrome 14%
  – Alopecia 12%


Sunitinib: Skin coloration

• Yellow skin coloration appears after 1 week of treatment in patients (30%)
• Increased in intensity at higher doses
• Associated with a yellow coloration of urine due to the excretion of the drug and metabolites
• May be due to drug itself (yellow in color)

Sorafenib tosylate
(BAY 43-9006/Nexavar®)

• Indications
  – 2005: Advanced renal cell cancer
  – 2007: Hepatocellular carcinoma
  – 2013: Metastatic thyroid cancer

• Inhibits
  – Ras/Raf signaling pathway
  – VEGFR1,2,3
  – PDGFR-β
  – FLT3
  – c-KIT
  – RET

Sorafenib tosylate
(BAY 43-9006/Nexavar®)

• Hypertension (VEGFR inhibition): 23%
• Dermatologic reactions
  – Facial/Scalp erythema/dysesthesias (~60%)
  – Hand-foot syndrome (37-50%)
  – Alopecia (~30%)
  – Subungual hemorrhages (~30%)
  – Pruritus (19%)
  – Xerosis (11%)
  – Mucositis (10-20%)
  – “Sorafenib dermatitis”
  – Erythema multiforme

**Sorafenib: Facial/Scalp erythema**

**Sorafenib: Subungual hemorrhages**
Sorafenib: Mucositis

Sorafenib dermatitis
Sorafenib: EM-LIKE ERUPTION

Sorafenib: Acral erythema/hand-foot syndrome
BRAF inhibitors

- **Vemurafenib, Dabrafenib**
  - Photosensitivity (V >> D)
  - Folliculocentric rash (68%)
    - Emollients → Anti-H<sub>2</sub> → top steroids → po steroids
  - Hand/foot syndrome (6-60%)
  - Eruptive nevi, 2<sup>nd</sup> melanoma
  - Seb derm-like eruption
  - Epidermal neoplasms
    - Verrucous keratoses
    - Squamous cell carcinoma/keratoacanthoma type (20-30%)
      - Associated with older age


Well-differentiated SCCs during BRAF inhibitor therapy

MacDonald et al. JAAD 2015;72:221.
BRAF inhibitor-associated SCC

- Mechanism
  - RAS mutations in 60% of vemurafenib pts.
  - Paradoxical increase in MAPK signaling in cells harboring mutated HRAS
  - Suggest that MEK inhibition might abrogate this potentiation


MEK/ERK inhibitors

- Cobimetinib (Cotellic™); Trametinib (Mekinist);
- Concurrent use with BRAF inhibitor therapy associated with decreased risk of KA/SCC
- Exanthematous morbilliform eruption
- Cutaneous adverse events similar to EGFRI
  - Acneiform eruption
  - Paronychia
  - Alopecia (mild)
  - Xerosis
BRAF inhibitor-associated panniculitis
Dabrafenib vs. vemurafenib

Table 1. Dermatologic Adverse Effects of Dabrafenib vs. Vemurafenib

<table>
<thead>
<tr>
<th>Effect</th>
<th>Dabrafenib Monotherapy (n = 115)</th>
<th>Vemurafenib (n = 110)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acneiform reaction</td>
<td>9 (8.2%)</td>
<td>1 (0.9%)</td>
<td>.31</td>
</tr>
<tr>
<td>Acneiform keratin</td>
<td>32 (26.5%)</td>
<td>11 (15.5%)</td>
<td>.47</td>
</tr>
<tr>
<td>Acneform (ulceration)</td>
<td>14 (11.7%)</td>
<td>2 (1.8%)</td>
<td>.08</td>
</tr>
<tr>
<td>BCC</td>
<td>18 (15.5%)</td>
<td>7 (6.4%)</td>
<td>.54</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>15 (12.8%)</td>
<td>6 (5.5%)</td>
<td>.53</td>
</tr>
<tr>
<td>Cutaneous SCC</td>
<td>31 (26.1%)</td>
<td>13 (11.9%)</td>
<td>.24</td>
</tr>
<tr>
<td>Drug reaction</td>
<td>4 (3.5%)</td>
<td>4 (3.6%)</td>
<td>.602</td>
</tr>
<tr>
<td>Erythema</td>
<td>8 (6.7%)</td>
<td>6 (5.5%)</td>
<td>.67</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>8 (6.7%)</td>
<td>5 (4.5%)</td>
<td>.17</td>
</tr>
<tr>
<td>Granuloma annulare</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>.58</td>
</tr>
<tr>
<td>Gross ulceration</td>
<td>15 (12.7%)</td>
<td>14 (12.7%)</td>
<td>.67</td>
</tr>
<tr>
<td>Hair loss</td>
<td>17 (14.3%)</td>
<td>7 (6.4%)</td>
<td>.45</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (10.4%)</td>
<td>1 (0.9%)</td>
<td>.76</td>
</tr>
<tr>
<td>Inflammation</td>
<td>8 (6.7%)</td>
<td>4 (3.6%)</td>
<td>.59</td>
</tr>
<tr>
<td>Keratosis palmaris</td>
<td>2 (1.7%)</td>
<td>2 (1.8%)</td>
<td>.96</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3 (2.5%)</td>
<td>4 (3.7%)</td>
<td>.03</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1 (0.8%)</td>
<td>14 (12.7%)</td>
<td>.00024</td>
</tr>
<tr>
<td>Pretaric hypertens</td>
<td>47 (39.5%)</td>
<td>14 (12.7%)</td>
<td>.05</td>
</tr>
<tr>
<td>Primary melanoma</td>
<td>3 (2.5%)</td>
<td>0</td>
<td>.14</td>
</tr>
<tr>
<td>Venous ulceration</td>
<td>14 (12.4%)</td>
<td>8 (7.3%)</td>
<td>.12</td>
</tr>
<tr>
<td>Venous keratoma</td>
<td>79 (16.6%)</td>
<td>26 (23.2%)</td>
<td>.55</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (4.2%)</td>
<td>1 (0.9%)</td>
<td>.70</td>
</tr>
</tbody>
</table>

BRAF inhibitor-associated panniculitis

- Management: NSAIDS, low dose prednisone

Targeted anti-neoplastic skin AEs

Conclusion

• New drug ‘allergies’ are challenging

• Targeted treatments
  – Mechanistic approach to understanding adverse reactions

• New therapeutic options for chronic, difficult diseases
  – Severe psoriasis
  – Fungal infection
  – Melanoma

• Long-term treatment → management dilemma