New Drugs – New Dystrophies

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Disclosures

- Spruce Health – Salary, ownership interest
- Biopelle Inc. – Consultant
Objectives

• Describe the most common nail changes seen in cancer patients being treated with new targeted agents:
  – EGFR and HER2 inhibitors
  – MEK inhibitors
  – mTOR inhibitors
  – BRAF inhibitors
  – Multikinase inhibitors

• Appreciate the importance of monitoring for and treating infection in cancer patients with nail changes

• Improve communication with oncologists regarding cancer treatment-related adverse events
The “Old” Drugs
Nails: Innocent Bystanders

- Rapidly dividing nail matrix sensitive to antimitotic chemotherapeutic agents
- Usually temporary changes
- Beau’s lines, onycholysis, pigmentation
Cytotoxic Chemotherapy Toxicities
New Drugs – New Toxicities
## Epidermal Growth Factor Receptor Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Year Approved</th>
<th>Type</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Iressa</td>
<td>2003/2015</td>
<td>Reversible TKI of EGFR</td>
<td>NSCLC with selected mutations</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux</td>
<td>2004</td>
<td>Human-mouse chimeric monoclonal antibody to EGFR</td>
<td>Colorectal, head &amp; neck SCC</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Tarceva</td>
<td>2005</td>
<td>Reversible TKI of EGFR</td>
<td>NSCLC, pancreatic</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix</td>
<td>2006</td>
<td>Fully human monoclonal antibody to EGFR</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Tykerb</td>
<td>2007</td>
<td>TKI of EGFR and HER2</td>
<td>Breast</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Caprelsa</td>
<td>2011</td>
<td>TKI of EGFR, VEGF, and others</td>
<td>Medullary thyroid</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Gilotrif</td>
<td>2013</td>
<td>Irreversible TKI of EGFR, HER2, and HER4</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Tagrisso</td>
<td>2015</td>
<td>TKI of EGFR with T790 mutation more than wild-type</td>
<td>T790M mutation-positive NSCLC</td>
</tr>
</tbody>
</table>

**TKI = tyrosine kinase inhibitor**  
**NSCLC = non-small cell lung cancer**  
**EGFR = epidermal growth factor receptor**

Epocrates.com  
Cancer.org
## HER2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Year Approved</th>
<th>Type</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Tykerb</td>
<td>2007</td>
<td>TKI of EGFR and HER2</td>
<td>Breast</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
<td>2012</td>
<td>Humanized monoclonal antibody for HER2</td>
<td>Breast</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>1998</td>
<td>Monoclonal antibody for HER2</td>
<td>Breast, gastric</td>
</tr>
</tbody>
</table>

Cancer.org
Epocrates.com
# MEK Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Year Approved</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trametinib</td>
<td>Mekinist</td>
<td>2013</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Cobimetinib</td>
<td>Cotellic</td>
<td>2015</td>
<td>Metastatic melanoma</td>
</tr>
</tbody>
</table>

Cancer.org  
Epocrates.com  
## BRAF Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Year Approved</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>Zelboraf</td>
<td>2011</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>Tafinlar</td>
<td>2013</td>
<td>Metastatic melanoma</td>
</tr>
</tbody>
</table>
Timeline of Cutaneous Effects of EGFR Inhibitors
EGFR and MEK Inhibitors
Effects on the Periungual Tissue

- Paronychia
- Fissures
- Pyogenic granuloma-like lesions
- Periungual lesions with EGFR inhibitors
  - All-grade 17.2%
  - High-grade 1.4%

EGFR and MEK Inhibitors
Effects on the Periungual Tissue
EGFR and MEK Inhibitors
Effects on the Periungual Tissue - Pathogenesis

• Inhibition of keratinocyte proliferation and increased apoptosis
• Periungual epidermis thins possibly allowing piercing of paronychium by lateral nail plate causing foreign body-type reaction
• Effect of intracellular retinoid metabolism?

EGFR and MEK Inhibitors
Effects on the Periungual Tissue - Pathogenesis
EGFR and MEK Inhibitors
Effects on the Periungual Tissue - Treatment

- CULTURE!!!
- High potency topical steroids
- Intralungal steroids
- Silver nitrate, cryotherapy, desiccation for excessive granulation tissue
- Nail avulsion
- Tetracycline antibiotic
- Antibacterial soaks
- Topical adapalene gel?

Osimertinib and Paronychia

- Newest EGFR inhibitor which has less affinity for wildtype EGFR
EGFR and MEK Inhibitors
Effects on the Periungual Tissue - Infections

• Retrospective analysis of 42 cultures of paronychia
• Gram positive 72%
• Gram negative 23%
• Fungi 4%
• Authors recommend cephalosporin or fluoroquinolone for empiric therapy
• Consider tetracycline antibiotic

Combination of Pertuzumab and Trastuzumab May Increase Infection Risk

• 18 patients with 21 infections
• All *Staphylococcus*
EGFR Inhibitors and Infections

<table>
<thead>
<tr>
<th>Gram Stain</th>
<th>Methicillin-susceptible Staphylococcus aureus (MSSA) (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess, Bacteriology Culture</td>
<td></td>
</tr>
<tr>
<td>Comments: Moderate</td>
<td></td>
</tr>
<tr>
<td>Resulting Agency</td>
<td>Moses</td>
</tr>
<tr>
<td>Susceptibility</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;2 mcg/mL Resistant</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;4 mcg/mL Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;=2 mcg/mL Sensitive</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>0.5 mcg/mL Sensitive</td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td>&gt;8 mcg/mL Resistant</td>
</tr>
<tr>
<td>Trimethoprim + Sulfamethoxazole</td>
<td>&lt;=0.5/9.5 mg/mL Sensitive</td>
</tr>
</tbody>
</table>
EGFR and MEK Inhibitors
Effects on the Nail Plate

- Brittle nails
- Nail cracking
- Onychoschizia
- Onychorrhexis
- Onycholysis
- Due to EGFR inhibition in matrix keratinocytes or inflammation from paronychia?
EGFR and MEK Inhibitors
Effects on the Nail Plate - Treatment

- Gentle nail care and protection
- Poly-ureaurethane, 16%
- Hydrosoluble nail lacquer
- Tazarotene cream
- Urea
- Biotin
- Nail polish
mTOR Inhibitors

- Everolimus and temsirolimus
- Nail plate thinning
- Onychodystrophy
- Brittle nails
- Distal onycholysis
- Xanthochromia

Sorafenib and Sunitinib

• Multikinase inhibitors
• Sorafenib
  – Renal cell carcinoma
  – Hepatocellular carcinoma
• Sunitinib
  – Renal cell carcinoma
  – Gastrointestinal stromal tumor
Sorafenib and Sunitinib

- Splinter hemorrhages
- Sorafenib – 70%
- Sunitinib – 30%
- First 2 months of treatment
- Spontaneous resolution

Imatinib

- Approved for Ph+ CML, Ph- ALL, MDS, systemic mastocytosis, hypereosinophilic syndrome, DFSP, Kit+ GIST
- Inhibits Bcr-Abl, PDGF, SCF, c-Kit tyrosine kinases
- Can cause nail hyperpigmentation

BRAF Inhibitors and the Nails

- Vemurafenib
  - Paronychia – 50%
  - Brittle nails – 40%
  - Onycholysis – 40%

- Dabrafenib
  - Onycholysis 10%

# Nail Changes Grading

<table>
<thead>
<tr>
<th>Condition</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nail Discoloration</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail Loss</td>
<td>Asymptomatic separation of the nail bed from the nail plate or nail loss</td>
<td>Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail Ridging</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nail Infection</td>
<td>Localized, local intervention indicated</td>
<td>Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)</td>
<td>IV antibiotic, antifungal or antiviral intervention indicated; radiologic or operative intervention indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>Nail fold edema or erythema; disruption of the cuticle</td>
<td>Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)</td>
<td>Surgical intervention or IV antibiotics indicated; limiting self care ADL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nail Care Tips for Patients

• Watch for signs of infection – pain, drainage, green discoloration
• Do not trim cuticles
• Keep hands well moisturized and wear gloves when doing house work
• Cotton gloves at night can help increase penetration of moisturizers and topical medications
• Manicures are OK with sterile instruments and avoid UV dryers
Conclusions

• New targeted cancer therapies have common effects on the nails and periungual tissue
• Infection is an important consideration in these patients
• Use CTCAE grading to communicate severity to the treating oncologists
• Dermatologists are an increasingly important part of the oncology treatment team
Thank You!

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