Faculty: Curtis Kellett

Relationships with Commercial Interests:

- Advisory board with Sanofi-Aventis 2012
- Honoraria received for Amgen Presentations given 2012 - 2014
Mitigating Potential Bias

- Presentation today focuses side effects and their management, not directing choice of chemotherapy
Objectives

- List some common dermatological toxicities associated with chemotherapy treatment
- Review the structure and function of skin
- Describe possible management strategies for pruritus and xerosis
- Discuss the difference between Hand-Foot Skin Reaction and Hand-Foot Syndrome and offer a treatment plan
- Outline appropriate preventative and supportive care for a patient with a papulopustular EGFR-associated rash
- Identify a possible treatment algorithm for the management of paronychia
Why is this topic important?

- Chemotherapy generally targets rapidly dividing cells and consequently is toxic to organ systems with high metabolic rates
  - Bone Marrow
  - Hair
  - Nails
  - Skin
  - Gastrointestinal mucosa

- With the advent of multi-agent chemotherapy regimens, drug reactions have become increasingly difficult to attribute to a single agent, especially since multiple agents may be associated with the same dermatological toxicity

Chemotherapy Agents Causing Dermatologic Toxicity and Rash

- Actinomycin
- Aldesleukin
- Amifostine
- Arsenic trioxide
- Asparaginase
- Azacitidine (pediatric)
- Bendamustine
- Bicalutamide
- Bortezomib (SC route)
- Brentuximab vedotin
- Cetuximab
- Cladribine
- Dasatinib
- Doxorubicin, Liposomal
- Erlotinib
- Gefitinib
- Gemcitabine
- Ixabepilone
- Imatinib
- Irinotecan
- Lapatinib
- Levasimole
- Methotrexate
- Ofatumumab
- Oprelvekin
- Oxaliplatin
- Palifermin
- Panitumumab
- Pemetrexed
- Pertuzumab
- Procarbazine
- Sorafenib
- Sunitinib
- Temozolomide
- Temsirolimus
- Thalidomide
- Topotecan
- Trimetrexate
- Vandetanib
- Vemurafenib
Dermatological Toxicities

- Rash
  - Maculopapular Rash (Morbilliform Eruption)
  - Dermatomyositis Like-Rash
  - Folliculitis
  - Acneform eruptions
  - Scleroderma-like changes
  - Psoriasis - Worsening
  - Sclerodermiform Dermatitis
  - Seborrheic Dermatitis Like-Rash (Dandruff)
  - Seborrheic inflammation or Actinic Keratoses
  - Pseudocellulitis

- Modifications of Hair
  - Alopecia
  - Tricomegaly
  - Depigmentation
  - Increased growth

- Extravasation
- Pigmentary changes
- Mucositis
- Photosensitivity / UV Recall
Dermatological Toxicities

- **Nail changes / Toxicity**
  - Mee’s lines (transverse white lines)
  - Beau’s lines (transverse grooves or lines)
  - Muehrcke’s lines multiple, white, transverse pale bands separated by strips of pink nail bed which fade on digital compression)
  - Melanonychia
  - Hyperpigmentation
  - Leukonychia

- **Onycholysis**
- **Paronychia**
- **Subungual Hemorrhages**

- **Radiation recall**
- **Acral Erythema (Hand-foot syndrome)**
- **Ulcers**
- **Xerosis / Pruritis**
- **Etc.**
Select Skin Toxicities of Cancer Therapy

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17 March 2015
Skin Structure - Epidermis

- Epidermis
  - thin outer layer of the skin
  - contains no blood vessels and relies on the dermis for its nutrients and waste removal
  - made up of layers of cells (basal cells and squamous cells) that work together to continually rebuild the surface of the skin
  - also includes 2 other types of specialized cells: Langerhans cells (involved in immune response) and Merkel cells (believed to play a role in making the skin sensitive to touch).

- The basal cell layer
  - deepest part of the epidermis
  - Basal cells continually divide, producing new cells that undergo a maturing, or keratinisation, process as they push the older cells toward the surface of the skin
  - These older cells eventually become flattened squamous cells

Skin Structure - Epidermis (2)

- Epidermis
  - The squamous cell layer
    - located above the basal cell layer and occupies the major part of the epidermis
    - main cells are called keratinocytes
    - contain keratin, a tough substance that helps to protect the skin from injury
  - As keratinocytes mature and move toward the surface of the skin, they undergo gradual changes in composition and appearance
  - Shortly before they reach the surface, the cells die and take on a scale-like appearance (squamous cells)
  - The surface of the skin is covered in dead cells, which are shed and replaced every 3-4 weeks by the newly divided cells in the basal cell layer that will be pushed up
Skin Structure (2)

- **Dermis**
  - second layer of the skin, beneath the epidermis
  - thickest of all 3 layers
  - made up of a papillary layer and a reticular layer
  - Collagen and elastin are produced by fibroblasts in the dermis to provide structure to the skin
  - Most of the skin’s specialized structures are found in the dermis: blood vessels, lymph vessels, hair follicles, sweat glands, sebaceous glands and nerve endings

- **Subcutis**
  - Beneath the dermis lies a fat layer known as the subcutis or hypodermis
  - made up mainly of adipose tissue
  - conserves the body’s heat and protect the organs of the body

Functions of the skin

- Temperature regulation
- Control fluid loss
- Sensation - nerve receptors sense cold, heat, pain and pressure
- Storing water, fat and Vitamin D
- Protection
  - from heat, sunlight, injury and infection

M.T. is a 54 year old female diagnosed with a Metastatic Gastrointestinal Stromal Tumour

Initially treated with 1st line imatinib, however recent imaging shows disease progression despite dose escalation

Offered 2nd line treatment with sunitinib
Patient Case - M.T.

- At a follow-up visit 4 weeks later, M.T. is managing well on the sunitinib, but complains of increasingly dry, itchy skin
What are we going to do for her?
Pruritis
Agents associated with pruritis:

- Aldesleukin
- Asparaginase
- Bevacizumab
- Cetuximab
- Erlotinib
- Gefitinib
- Interferon
- Panitumumab
- Sorafenib
- Sunitinib
- Thalidomide
Pruritis - Management

- Preventative: gentle skin care instructions

- Treatment
  - Topical agents included medium- to high-potency steroids
    - triamcinolone acetonide 0.025%, desonide 0.05%, fluticasone propionate 0.05% or alclometasone 0.05%) or,
    - menthol 0.5%-pramoxine 1%-doxepin
  - Systemic
    - oral non-sedating second-generation antihistamines (loratadine, etc.) first line
    - gabapentin, pregabalin or doxepin as second line agents if antihistamines fail
    - may want to have patient take sedating antihistamines at bed time*

Adapted from:
Pruritis - Management (2)

- Pilot study in 2012
- 45 solid tumour patients with refractory pruritis
  - Erlotinib and cetuximab were most-frequently offending agents
- Aprepitant (125 mg day 1, then 80 mg on day 3 and 5) improved symptoms

Accompanying editorial highlights concern over drug-drug interaction between aprepitant and erlotinib (or other CYP 3A4-metabolized tyrosine kinase inhibitors)

Xerosis
Xerosis

- Very common adverse effect
  - Sorafenib & sunitinib can lead to xerosis in up to 30% of patients
  - EGFR inhibitors can cause in up to 35% of patients
- Gradually develops over weeks with onset around 30 to 60 days or more
- Presents as dry, scaly and itchy skin which is more pronounced in older patients and those with a history of atopic eczema
- Can progress to chronic xerotic dermatitis with risk of being secondarily infected with S. aureus or Herpes simplex virus
- Xerosis on the hands or feet can lead to painful fissures in the tips of fingers and / or toes
Agents associated with xerosis:

- Bevacizumab
- Cetuximab
- Erlotinib
- Fluorouracil
- Gefitinib
- Panitumumab
- Sorafenib
- Sunitinib
- Thalidomide
- Tretinoin
Xerosis - Management

Prevention:

▶ Use tepid water, minimize showering and use bath oil or mild moisturizing soaps that do not have fragrances or perfumes

▶ Avoid extreme temperatures (severe cold, dry weather or significant heat or direct exposure to sun

▶ Refrain from using alcohol-containing lotions or skin products

Adapted from:
Xerosis - Treatment

Grade 0:
- prophylactic therapy with PABA-free sunscreen (SPF > 30); moisturizing creams and gentle skin care instructions (alcohol-free)

Grade 1:
- Continue anticancer agent at current dose and monitor patient for change in severity (Reassess in 2 weeks)
- OTC moisturizing cream (occlusive - usually packaged in a jar or tub) or ointment to face BID AND ammonium lactate 12% cream to body BID

Grade 2:
- Continue anticancer agent at current dose and monitor patient for change in severity (Reassess in 2 weeks)
- OTC moisturizing cream or ointment to face BID AND ammonium lactate 12% cream to body BID OR salicylic acid 6% cream to body BID

Adapted from:
Xerosis - Treatment (2)

Grade 3:

- Dose modify anticancer agent per package insert (PI)
- Obtain cultures (bacterial / viral) if infection is suspected and continue treatment with:
  - OTC moisturizing cream or ointment to face BID AND Ammonium lactate 12% cream to body BID OR Salicylic acid 6% cream to body BID AND Triamcinolone 0.25% cream to eczematous areas BID
- Reassess patient in 2 weeks; if reaction is worse or not improve, dose interruption and / or discontinuation per PI may be required

Adapted from:
Fissures

Treatment of Fissures

- Thick moisturizers or zinc oxide creams
- Dakin’s solution soaks (1/4 cup household bleach in 3 gallons of water) may prevent infection
- Liquid glues (Superglue® or Liquid Band-Aid®) can seal the cracks & keep them from worsening or getting infected
- Propylene glycol 50% solution and salicylic acid 10% ointment may also be used
- For painful, erythematous areas steroid tape and hydrocolloid dressings are recommended
- Limited evidence for silver nitrate or potassium permanganate foams or topical antibiotics
- Oral antibiotics may be required if infection worsens despite topical treatment

Patient case - L.D.

- L.D. is a 62 year old male with KRAS wild-type, metastatic colorectal cancer
- He has progressed on 1st line FOLFIRI + Bevacizumab
- Eager to continue with additional treatment, but is looking for a little bit more flexibility with his time
  - Has a cottage on the lake
- Started on XELOX chemotherapy as 2nd line
Patient case - L.D. (2)

- L.D. tolerates his first cycle well with some mild nausea and dry skin

- Calls back to clinic nurse on Day 7 of Cycle #2 indicating that the palms of his hands are now reddened and somewhat sore
What is happening to L.D.?
What are we going to do for him?
Hand-foot syndrome

- Hand-foot syndrome (palmar-plantar erythrodysesthesia) is a common adverse event, with moderate to severe cases seen in 11-17% of patients who receive capecitabine¹

- Effective management of hand-foot syndrome is important as, in severe cases, it can lead to permanent treatment discontinuation and to secondary infections²

¹Xeloda® (capecitabine) [package insert]. Nutley, NJ: Roche Laboratories; 2009
Chemotherapy Agents Causing Acral Erythema / Palmar-Plantar Erythrodysesthesies

- Aldesleukin
- Amifostine
- Bleomycin
- Capecitabine
- Cisplatin
- Cyclophosphamide
- Cytarabine
- Daunorubicin
- Daunorubicin, Liposomal
- Docetaxel
- Doxorubicin
- Doxorubicin, Liposomal
- Epirubicin
- Erlotinib (erythema)
- Etoposide
- Fluorouracil
- Hydroxyurea
- Idarubicin
- Lapatinib
- Lomustine
- Melphalan
- 6-Mercaptopurine
- Methotrexate
- Mitomycin
- Oxaliplatin
- Paclitaxel
- Regorafenib
- Sorafenib
- Sunitinib
- Tegafur
- Thiotepa
- Vinorelbine

Hand-Foot Syndrome vs Hand-Foot Skin Reaction

“Despite similarities in certain clinical characteristics, such as involvement of palms and soles, dose dependence, pain, and resolution of symptoms upon discontinuation of the offending drug, HFSR appears to be a distinct entity from hand-foot syndrome (HFS) associated with conventional cytotoxic agents (doxorubicin, 5-fluorouracil, and capecitabine [Xeloda]).”
HFSR

HFSR is seen with multikinase inhibitors, including sorafenib and sunitinib

- seen within the first 2 to 4 weeks after initiation

- Presents with dysesthesias, erythema or paresthesias involving the palms and soles with blisters which are followed by thick hyperkeratotic, tender lesions

Lesions arise in areas of friction and/or trauma including the flexural surface of interphalangeal joints, distal phalanges or heels and may significantly impact weight-bearing ability and mobility of patients.

Loss of repair mechanisms by endothelial cells and fibroblasts, when combined with daily trauma may result in the characteristic palmoplantar symptoms.
Management of HFSR

Preemptive strategies are crucial in the management of HFSR and include:

- Performing full body exam to locate hyperkeratotic regions on palms / soles and removal of all calluses
- Wearing thick cotton gloves and / or slippers or socks
- Using moisturizing creams that contain keratolytics such as ammonium lactate or urea prior to and during treatment
- Avoiding
  - Exposing skin to hot water
  - Friction or trauma for the first 2 to 4 weeks of therapy
  - Rigorous exercise (especially during first 4 weeks of therapy)
  - Tight fitting shoes
  - Excessive pressure when applying lotions
Hand-Foot Syndrome (palmar-plantar erythrodysesthesia)

- Seen with many conventional cytotoxic chemotherapies, including capecitabine, cytarabine, docetaxel, doxorubicin, fluorouracil, methotrexate, and pegylated liposomal doxorubicin

- More diffuse regions of edema and erythema than seen with HFSR

- Longer exposure to drug appears to increase incidence; eg. continuous infusion fluorouracil has higher incidence versus bolus administration; liposomal doxorubicin has higher incidence than doxorubicin

- Symptom onset is quite variable and may range from a few days to up to 10 months after therapy initiation
Hand-Foot Syndrome (2)

- Initial symptom is paresthesias followed by symmetrical painful erythema and edema of the palms and soles after 3 to 4 days
  - if not managed the lesions may blister, desquamate, form crusts, ulcerate or progress to epidermal necrosis

- Conflicting data regarding use of pyridoxine (vitamin B6) for prevention and/or treatment of HFS
  - randomized controlled trial to prevent capecitabine induced HFS was negative so not recommended

- Use of corticosteroids is also conflicting

- Regional cooling strategies also lack adequate evidence to support use
Management of HFSR and HFS

With maintenance skin care and eventual dose reductions, L.D. completes 6 cycles of XELOX chemotherapy.

Unfortunately, repeat CT scans done at that time indicate that his cancer is progressing.

His oncologist offers him 3rd line chemotherapy with Cetuximab.
Patient case - L.D. (6)

Which of the following answers below is the most appropriate to manage his EGFR inhibitor-associated rash?

a) L.D. should receive prophylactic rash management with hydrocortisone 1% with moisturizer, sunscreen, doxycycline 100 mg BID and tazarotene topically

b) L.D. should receive prophylactic rash management with hydrocortisone 1% with moisturizer, sunscreen, and doxycycline 100 mg BID

c) Once he develops a rash, he should receive treatment with medium-to high-potency topical steroids, clindamycin 1%, oral antibiotics and tazarotene topically

d) Once he develops a rash, he should receive treatment with medium-to high-potency topical steroids, clindamycin 1% and oral antibiotics

Adapted from:
## Incidence of Dermatological Toxicities

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Incidence (All Grades)</th>
<th>Incidence (Grade 3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>76% - 88%</td>
<td>1% - 17%</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>91%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* Note: Incidences reported for Monotheray

Panitumumab Product Monograph. Amgen Canada, December 2010;
Cetuximab Product Monograph. Bristol-Myers Squibb, May 2010
Papulopustular (Acneiform) Rash

- **Multikinase inhibitors**
  - Presents with a rash similar to the EGFR inhibitors, but severity is usually less
  - Incidence is 40% receiving sorafenib and 20% of those receiving sunitinib

- **EGFRs play an important role in the development, integrity and physiology of normal skin via the regulation of keratinocyte proliferation, differentiation and survival**
  - The direct inhibition of EGFRs is thought to be the underlying cause of the rash
  - It is thought that exposure of epithelial cells to medication leads to an increased synthesis of a variety of chemokines that recruit inflammatory cells, including leukocytes and neutrophils leading to an inflammatory response
Preemptive skin treatment:

Daily Skin Tx (Day -1 through Week 6)
- Skin moisturizer
- Sunscreen (PABA free, SPF 15, UVA and UVB protection)
- Topical steroid (1% hydrocortisone cream)
- Doxycycline 100 mg twice per day

Reactive skin treatment:

- Appropriate management of emergent skin toxicity - could be administered at any time during weeks 1 to 6
- Patients choice of skin moisturizer and/or sunscreen at any time during the study
Management of Dermatological Toxicities: STEPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Emptive Skin Treatment</th>
<th>Reactive Skin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Patients with grade 2 or higher skin toxicity*</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Odds ratio†</td>
<td>0.3</td>
<td>0.1 to 0.6</td>
</tr>
<tr>
<td>95% CL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>95% CL</td>
<td>11 to 35</td>
<td>26 to 54</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>95% CL</td>
<td>0 to 13</td>
<td>10 to 33</td>
</tr>
<tr>
<td>Total panitumumab doses administered during the skin treatment period</td>
<td>155</td>
<td>141</td>
</tr>
<tr>
<td>Total panitumumab doses delayed during the skin treatment period†</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Lacouture M E et al. JCO 2010;28:1351-1357
Management of EGFR toxicity

- Phase III study of metastatic colorectal cancer patients (2007)
  - 48 patients with cetuximab-associated skin rash
  - Randomly assigned to prophylactic minocycline PO vs placebo and topical tazarotene 0.05% cream applied BID to either the left or right side of the face for 8 weeks

Management of EGFR toxicity

Results

- Total facial lesion counts were significantly lower in patients receiving minocycline at weeks 1 to 4
- Lower proportion receiving minocycline reported moderate to severe itch vs placebo at week 4 (20% vs 50%, p=0.05)
- Minocycline patients had a trend toward lower frequency of moderate to severe rash versus patients on placebo (20% vs 42%, p=0.13)
- Differences in total facial lesion counts and subjectively assessed itch were diminished by week 8

Management of EGFR toxicity

- Cetuximab treatment was held due to grade 3 skin rash in four patients in the placebo arm vs none in the minocycline arm

- No clinical benefit was seen for tazarotene;
  - significant irritation leading to therapy discontinuation in 1/3 of patients

- Authors conclude that oral minocycline may be useful to decrease severity of acneiform rash during the first 4 weeks of cetuximab treatment

Canadian Recommendations for Management of EGFR Skin Rash

Table 3
Papulopustular (acneiform) rash recommendations

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Not recommended</th>
<th>Level of evidence</th>
<th>Recommendation grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive (weeks 1–6 and 8 of EGFR initiation)</td>
<td>Hydrocortisone 1% cream with moisturizer and sunscreen twice daily</td>
<td>Pimecrolimus 1% cream</td>
<td>I²</td>
</tr>
<tr>
<td>Topical</td>
<td>Tazarotene 0.05% cream</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Sunscreen as single agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minocycline 100 mg daily</td>
<td>Tetracycline 500 mg bid</td>
<td>I²</td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg bid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient case – L.D. (7)

- L.D. receives his prescriptions for preventative skin care and begins receiving Cetuximab infusions weekly

- He is tolerating treatment well, however at his 8 week visit he reports having a sore toe
Patient case - L.D. (8)
Chemotherapy agents causing paronychia

- Capecitabine
- Cetuximab
- Docetaxel
- Erlotinib
- Fluorouracil
- Gefitinib
- Methotrexate
- Paclitaxel
- Panitumumab
Paronychia (periungual inflammation)

- Associated with all EGFR inhibitors and can be seen in up to approximately 15% of patients.
- Toxicity manifests later in treatment, usually occurring after 1 to 2 months of therapy.
- Progresses from erythema to painful inflammation and swelling of the skinfolds and tissues surrounding the finger or toe nail.
- Patients then develop pus-filled granuloma-like lesions around the affected nail(s) which are very painful; may mimic an ingrown nail.
- Secondary infection with S. aureus or gram-negative bacteria may occur.
Paronychia Management

Take Home Points

- Ongoing development of new chemotherapy agents and combinations have improved the survival of patients with cancer.

- Dermatological toxicities occur frequently with the use of chemotherapy.

- Cutaneous reactions attributable to chemotherapy can result in patient morbidity and alteration of the treatment plan.

- Early recognition and treatment of the toxicity facilitates good symptom control, prevents treatment-related morbidity, and allows continuation of anti-cancer therapy.

2. http://i574.photobucket.com/al...
Questions?