Clinical Update on the Management of Dermatologic Toxicities

Theresa Stehmer, PharmD
Clinical Oncology Pharmacist
Duke University Hospital

Disclosure

- The speaker has no actual or potential conflicts of interest in relation to this presentation.
Objectives

1. Describe common dermatologic toxicities associated with chemotherapeutic agents with a focus on targeted agents and immune checkpoint antibodies.
2. Discuss management strategies for common dermatologic toxicities associated with chemotherapeutic agents with a focus on targeted agents and immune checkpoint antibodies.

Introduction

- Skin & mucosal reactions are among the most common toxicities associated with chemotherapeutic agents.
- Potential consequences of dermatologic toxicities:
  - Strongly impact on quality of life, sense of privacy, & physical/psychosocial/financial well-being
  - Can result in treatment modification &/or compromise clinical outcomes

Dermatologic Toxicities: Cytotoxics

- Cytotoxics are oldest & largest class of chemotherapy agents
- Exert anti-tumor effects by interfering with DNA replication
  - Affects both cancer cells **AND** rapidly dividing healthy tissues → including hair, skin, nails, & mucosa
- Results in several nonspecific dermatologic toxicities common to a majority of cytotoxics


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### Dermatologic Toxicities: Cytotoxics

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Common Agents</th>
<th>Management Strategies</th>
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</table>
| Mucositis           | antimetabolites, alkylating agents    | - Oral cryotherapy: topical ice chips/popsicles induce localized vasoconstriction prior to & during drug infusion; more effective for drugs with short $t_{1/2}$  
|                     |                                      | - Palifermin: keratinocyte growth factor; recommended for patients receiving high-dose chemotherapy + TBI in preparation for ASCT  
|                     |                                      | - Pain medications: topical viscous lidocaine often used, may need systemic opioids  |
| Alopecia            | 5-FU, MTX, alkylating agents, topoiso inhibitors, taxanes | - Scalp cooling: studied for alopecia prevention; data lacking, efficacy variable  
|                     |                                      | - Topical minoxidil: not useful for prevention of chemotherapy-induced alopecia, BUT can be used after completion to speed hair regrowth  |
| Onycholysis         | mitoxantrone, docetaxel, prolonged paclitaxel | - Aggressive photoprotection: recommended as preventative measure; onycholysis can be worsened by UV light  |
| Extravasation Injury| vesicants: blistering & tissue necrosis irritants: inflammatory response | - Intermittent icing: for irritant extravasations  
|                     |                                      | - IV Dexamethasone + icing: for anthracycline extravasations  
|                     |                                      | - SQ sodium thiosulfate + icing: for nitrogen mustard extravasations  
|                     |                                      | - Hyaluronidase + warm packs: for vinca alkaloid extravasations  |
| Hypersensitivity Reactions | taxanes, platinumis, edipophytotoxins, procarbazine | - Appropriate premedications given before chemotherapy  
|                     |                                      | - Established Hypersensitivity Protocols in place  
|                     |                                      | - Desensitization Protocols, if appropriate  |


TBI: total body irradiation; ASCT: autologous stem cell transplant  
5-FU: 5-fluorouracil; MTX: methotrexate
Dermatologic Toxicities: Cytotoxics

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<tr>
<td>Radiation Recall</td>
<td>anthracyclines, taxanes, gemcitabine, dactinomycin</td>
<td>- Removal of offending drug: primary treatment of radiation recall → may occur at any point after radiation therapy</td>
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<td></td>
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<td>- Symptomatic relief: topical/systemic corticosteroids, anti-inflammatory drugs, antihistamines</td>
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<tr>
<td>Hand-foot syndrome</td>
<td>liposomal doxorubicin, docetaxel, cytarabine, 5-FU, capecitabine</td>
<td>- Dosage interruption &amp;/or dose intensity modification: mainstay of treatment</td>
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<td></td>
<td></td>
<td>- Symptomatic relief: topical corticosteroids, wound care to prevent infection, topical keratolytic, pain control, frequent emollient use</td>
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<td>- Localized hypothermia: using cooling gloves &amp; socks during infusions to reduce HFS rates</td>
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<td>- Celecoxib: use in prevention of capecitabine-induced HFS has been studied → promising</td>
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<td>- Pyridoxine supplementation: efficacy in preventing HFS not clear cut</td>
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<td>- Avoidance of hot water, tight clothing/shoes, &amp; vigorous exercise also often recommended to prevent HFS</td>
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<tr>
<td>Hyperpigmentation</td>
<td>alkylating agents</td>
<td>- Majority of cases resolve spontaneously without treatment within months</td>
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Dermatologic Toxicities: Targeted Agents

- “On-target toxicities” (vs. “off-target toxicities”)
  - Mechanism-based toxicities shared by agents with the same target
  - Difficult to prevent → need to be managed proactively

- Dermatologic toxicities occur with inhibition of signaling proteins such as EGFR & VEGFR
  - Dose-dependent side effects that occur include:
    - Inflammation of pilo-sebaceous follicle → folliculitis
    - Alteration of skin barrier → hyperpigmentation, pruritus
    - Lesions of skin appendages → trichomegaly
Dermatologic Toxicities: EGFRIs

- EGFR regulates cell division, survival, apoptosis, motility, invasion, & gene repair and is normally expressed in:
  - Proliferating keratinocytes in basal layers of epidermis
  - Outer layers of the hair follicle
  - Pilosebaceous & eccrine sweat glands
  - Aberrantly activated in many epithelial tumors
- EGFRIs
  - mAbs: cetuximab (Erbitux™) & panitumumab (Vectibix™)
  - TKIs: erlotinib (Tarceva™), gefitinib (Iressa™), & lapatinib (Tykerb™)
  - Lapatinib: dual TKI (EGFR & HER2)
    - Also has less dermatologic toxicities than other EGFRIs

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<table>
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<tr>
<th>Toxicity</th>
<th>Onset</th>
<th>Description/Details</th>
<th>Management</th>
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</table>
| Papulopustular rash | 1-2 weeks             | - Very common (all Grades: 47-90%; Grade 3/4: 3-10%)  
- Pruritic erythematous papules & pustules  
- Located mostly in sebaceous-rich areas (i.e. face)  
- Often described as “acne-like,” but distinctly different  
- Dose dependent  
- mAbs cause more severe & frequent rash than TKIs  
- Risk factors: age, male, nonsmoker, UV exposure  
- Surrogate marker of drugs’ efficacy/clinical response | See Next Slide                                                                  |
| Xerosis & pruritus (post-rash) | 20-47 days            | - Seen in up to 35% of patients  
- Presents with pruritus & diffuse fine scaling  
- Tends to involve larger body surface area than rash  
- Can progress to chronic xerotic dermatitis if epithelial barrier disrupted  
- predisposed to superinfections | - Tepid water & mild (neutral pH) soap  
- Oil-in-water creams for symptomatic treatment  
- Pruritus: cool compresses, antihistamines, topical steroids, menthol lotion, pregabalin  
- Antibiotics (topical/systemic) for suspected secondary superinfection after cultured |
| Hair changes    | 7-10 weeks to many months | - Alopecia (scarring or non-scarring) in ~5% of patients  
- Textural changes  
- Curlier/thinner/more brittle hair  
- Trichomegaly  
- eyelash overgrowth, can be harmful | - Ophthalmologist referral with eye irritation  
- Clip long eyelashes |
| Paronychia      | 20 days – 6 months     | - Affects fingernails & toenails (mainly thumb/big toes)  
- Painful pyogenic granuloma-like lesions can form  
- bleed with minimal trauma & mimic ingrown nail  
- Inflammation of nailfolds increases risk of infection | - No frequent water immersion/harsh chemicals  
- Apply petroleum jelly frequently  
- Culture suspicious sites & treat with antibiotics  
- Wear well-fitting shoes to minimize trauma  
- Silver nitrate or ferric subsulfate  
- Daily soaks & cushioning for symptom relief |

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EGFR: epidermal growth factor receptor inhibitor  
mAb: monoclonal antibody, TKI: tyrosine kinase inhibitor  
HER2: human epidermal growth factor receptor 2
EGFRI Rash Treatment Algorithm

Grade 0
- **Prophylactice Therapy:** sunscreen ≥30 SPF; moisturizing creams; gentle skin care

Grade 1
- Continue anticancer agent at current dose & monitor for change in severity
- Treat with hydrocortisone 2.5% cream & clindamycin 1% gel every day
- Reassess after 2 weeks → if reactions worsen or do not improve, proceed to next step

Grade 2
- Continue anticancer agent at current dose & monitor for change in severity
- Treat with hydrocortisone 2.5% cream & doxycycline 100mg daily OR minocycline 100mg BID
- Reassess after 2 weeks → if reactions worsen or do not improve, proceed to next step

Grade 3/4
- 'Grade' based on %BSA affected by pustules/papules, symptoms, psychosocial impact, impact on ADL, & need for PO/IV antibiotics
- Prophylactic therapy **prior to chemotherapy** also recommended
  - Doxycycline 100mg BID + skin moisturizer + sunscreen + 1% hydrocortisone cream
  - Started 1 day prior to the start of chemotherapy, continue for 6 weeks
  - Based on trial with panitumumab → had >50% decrease in ≥Grade 2 toxicities & decreased impairment of quality of life


Dermatologic Toxicities: Multi-targeted TKIs

<table>
<thead>
<tr>
<th>Sorafenib (Nexavar™)</th>
<th>Sunitinib (Sutent™)</th>
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<tbody>
<tr>
<td>Targets</td>
<td>VEGFR-2, VEGFR-3, FLT-3, PDGFRβ, Raf</td>
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<tr>
<td>Dermatologic Toxicities</td>
<td>Rash/desquamation, HSFR, alopecia, stomatitis, dry skin, flushing, xerosis, pruritus, facial seborrheic dermatitis-like rash, subungual splinter hemorrhages, actinic keratoses (AC)</td>
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- HSFR – the most clinically significant & dose-limiting dermatologic toxicity associated with sorafenib & sunitinib
  - Pathophysiology not understood → dual VEGFR & PDGFR inhibition?
  - Onset within 6 weeks; presents with tender lesions +/- blisters, followed by thickened & hyperkeratotic lesions
  - Management:
    - Prophylaxis with heavy moisturizer or ammonium lactate 12%
    - Treatment can involve urea cream, clobetasol cream, or pain medications


HSFR: hand-foot skin reaction
Question #1

1. The incidence of rash associated with EGFR therapy increases significantly when combined with chemotherapy.

a. True
b. False

Dermatologic Toxicities: Immune Checkpoint Antibodies

- The immune system plays important role in controlling & eradicating cancer
- Antibody therapy developed against several negative immunologic regulators → CTLA-4 & PD-1/PD-L1
- CTLA-4: cytotoxic T lymphocyte-associated antigen 4
  - Essential role in maintaining normal immunologic homeostasis
  - Upregulated on plasma membrane; downregulates T-cell function
- PD-1/PD-L1: programmed cell death protein 1 pathway
  - Also negative regulator of T-cell activity
  - **PD-1 (unlike CTLA-4) is believed to inhibit effector T-cell activity in the effector phase within tissue and tumors

Ipilimumab irAEs

- Ipilimumab (Yervoy™)
  - Fully human mAb that blocks CTLA-4
- Immune checkpoint blockade does not JUST enhance tumor-specific immune responses
  - Nonspecific immunologic activation also causes unique side effects which have been termed irAEs
- Ipilimumab irAEs include dermatologic, gastrointestinal, hepatic, endocrine, & others (much less common)
- irAEs exhibit very characteristic pattern with timing:
  - Skin-related irAEs after 2-3 weeks
  - GI & hepatic irAEs after 6-7 weeks
  - Endocrinologic irAEs only after an average of ~9 weeks

Dermatologic Toxicities: Ipilimumab

- Rash
  - Differs from rash with targeted agents (i.e. EGFRIs)
  - Can be asymptomatic, or accompanied by pruritus
  - Appearance:
    - Typically reticular, erythematous, edematous, & maculopapular
    - Often located on trunk and/or extremities
    - Can coincide with regression of SQ disease
      - May be especially pronounced around nevi
  - Median time to onset: 3-4 weeks
  - Median time to resolution: 20 weeks
Ipilimumab Rash & Pruritus

Treatment Algorithms

**Treatment Algorithm for Rash**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Management</th>
<th>Follow-Up Every 1-2 Weeks</th>
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</table>
| Grade 1/2 | Topical corticosteroids & oral antihistamines | Resume ipilimumab IF: 
1. Dermatitis resolves or improves to mild (localized) symptoms
2. Systemic steroid dose is 7.5mg prednisone equivalent or less |
| Grade 3 | Hold ipilimumab Oral corticosteroids (1-2mg/kg/day) | If symptoms worsen, see management of grade 4 |
| Grade 4 | Permanently D/C ipilimumab Administer systemic corticosteroid therapy of 1-2mg/kg/day of prednisone | When dermatitis is grade 0/1, corticosteroid tapering should begin over a period of at least 1 month |

**Treatment Algorithm for Pruritus**

- Mild or Localized
  - Topical corticosteroids & antipruritics
- Intense or Widespread - Intermittent
  - Skin changes from scratching
    - Topical corticosteroids & oral antihistamines
- Intense or Widespread - Constant
  - Limiting self-care ADL or sleep
  - Oral antihistamines & corticosteroids
  - Consider gabapentin, pregabalin, mirtazapine, aprepitant


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Nivolumab & Pembrolizumab irAEs

- Nivolumab (Opdivo™)
  - Fully human mAb that blocks PD-1
- Pembrolizumab (Keytruda™)
  - Humanized mAb that blocks PD-1
- Spectrum of irAEs observed with PD-1 mAbs has been quantitatively similar to those seen with ipilimumab
  - HOWEVER, with fewer dose-limiting irAEs

Dermatologic Toxicities: Nivolumab & Pembrolizumab

- Rash
  - Similar to that seen with ipilimumab
  - Appearance: reticular, maculopapular, erythematous
  - Also found on the extremities or trunk
  - Onset within several weeks of treatment initiation
- Mucositis and/or dry mouth
  - Reported in small number of patients
  - Unique to PD-1 blockade?
- Management of rash & pruritus identical as with ipilimumab


Combination CTLA-4 & PD-1 Blockade

- Combination treatment with CTLA-4 & PD-1 mAbs currently under investigation
  - Distinct mechanisms of immune blockade
- Data exists for combination of ipilimumab + nivolumab AND ipilimumab + pembrolizumab
  - Higher rates of irAEs than ipilimumab, pembrolizumab, or nivolumab alone
  - No NEW toxicities seen
- Other trials ongoing...

Concurrent Immune Checkpoint mAbs & Targeted Agents

- Interest in exploring combinations of targeted agents with immune checkpoint mAbs (i.e. BRAF inhibitors)
- Toxicity profile of BRAF inhibitor + immune checkpoint mAb combination may vary with different agents
  - Phase I study evaluated concurrent vemurafenib + ipilimumab
    - Study closed due to high level of hepatic adverse events (↑ AST)
    - Several instances of grade 3 rash as well
  - Phase I study evaluated concurrent dabrafenib + ipilimumab +/- trametinib
    - No grade 3/4 ALT elevations or dose-limiting toxicities observed
    - Maculopapular rash among most common adverse events

Puzanov I et al. J Clin Oncol. 32:5s, 2014 (suppl; abstr 2511)

Question #2

2. What dermatologic toxicity is more common with nivolumab/pembrolizumab than ipilimumab?

   a. Acneiform rash
   b. Mucositis
   c. Maculopapular rash
   d. Pruritus
Questions?