PREVENTION AND MANAGEMENT OF SKIN TOXICITIES INCLUDING WHEN AND HOW TO COLLABORATE WITH DERMATOLOGISTS

Florian SCOTTE, MDPhD
Suresnes, France

Thanks to Vincent Sibaud for the pictures and teaching
DISCLOSURES

• Consultant / Advisory Boards / Speaker: Tesaro, Sanofi, Roche, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, AMGEN, Pierre Fabre Oncologie, Vifor Pharma

• Associations: ESMO, ASCO, MASCC, AFSOS, AESCO
A 58-year-old woman treated with eribulin therapy for a metastatic breast carcinoma. Two weeks after the second cycle, she developed blisters and painful bullous detachment in axillary areas and groin.

**Which is the most likely diagnosis?** (choose the single best response):

1. Toxic epidermal necrolysis
2. Glucagonoma
3. Staphylococcal scalded skin syndrome
4. Characteristic toxicity of chemotherapy
A 58-year-old woman treated with eribulin therapy for a metastatic breast carcinoma. Two weeks after the second cycle, she developed blisters and painful bullous detachment in axillary areas and groin.

Which is the most likely diagnosis? (choose the single best response):

1. Toxic epidermal necrolysis
2. Glucagonoma
3. Staphylococcal scalded skin syndrome
4. Characteristic toxicity of chemotherapy: Toxic Erythema of Chemotherapy
Toxic erythema of chemotherapy

- New clinically descriptive term to emphasize the overlapping features of toxic reactions observed with chemotherapy. May enhance communication and patient care.

- Toxic -nonallergic- drug reaction. Dose-dependent.

- Confined in contact and occlusive areas.

- **Docetaxel, paclitaxel, doxorubicin, etoposide, capecitabine, oxaliplatin, cytarabine, dactinomycin, thiopeta…..**

- **Overlapping terms (pubmed):** intertrigo dermatitis, intertriginous eruption of chemotherapy, flexural erythematous eruption, intertrigo-like eruption associated with chemotherapy, SDRIFE (symetric drug-related intertriginous and flexural exanthema), Chemotherapy-related bilateral dermatitis associated with eccrine squamous syringometaplasia…..

Toxic erythema of chemotherapy

Docetaxel, paclitaxel, doxorubicin, etoposide, capecitabine, oxaliplatin.....

Toxic *erythema of chemotherapy*

.....It is thought that accumulation/excretion of chemotherapy in sweat leads to direct toxic insults to eccrine glands and keratinocytes.....

Immune-mediated drug reactions...think about other associated drugs, or... !!!

Targeted therapies (sorafenib, regorafenib, dabrafenib, vemurafenib, bosutinib...), chemo (temozolomide, bendamustine), antibiotics, anticonvulsant drugs, analgesics.....
Chemo-induced (subacute) lupus erythematosus

5FU, capecitabine, pemetrexed, cisplatin, docetaxel......

UV-recall

Taxanes, methotrexate

Chemotherapy, scleroderma-like syndrome, pseudocellulitis

Gemcitabine, pemetrexed, taxanes, bleomycine......
Chemotherapy and inflammation of actinic keratoses

Fluorouracile, taxanes, cisplatine, capecitabine, doxorubicine......
**Toxic erythema of chemotherapy – key points**

- TEC is one of the most common skin toxic effects of high-dose chemo: taxanes+++; liposomal doxorubicin…

- **Site of predilection**: intertriginous zones, under dressings, pressure areas…; sweating, occlusive phenomenon and direct toxic effect

- Accurate diagnosis is critical for optimal management (topical steroids, dose reduction if needed…) and erroneous assignment of drug allergies (antibiotics…)

- Not every skin rash occurring with chemotherapy is a TEC….

Management: Toxic erythema of chemotherapy

- High-potency corticosteroids,
- celecoxib,
- antiperspirants (?),
- dose reduction,
- patient education
- and counselling……
Hand-Foot syndrome and chemotherapy

Liposomal doxorubicin, capecitabine, cytarabine, cyclophosphamide.....

Hand-foot skin reaction and targeted therapies

dual inhibition of VEGFR – PDGFR and/or BRAF protein

## Hand-foot skin reaction and targeted therapies (-nib)

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Incidence all grades (%)</th>
<th>Incidence High grades (%)</th>
<th>indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regorafenib (Stivarga ®)</strong></td>
<td>60,5</td>
<td>20,4</td>
<td><strong>VEGFR 1-3; PDGFR α-β; c-KIT; RAF; TIE-2; RET; P38 MAPK, FGFR-1</strong></td>
</tr>
<tr>
<td><strong>Sorafenib (Nexavar ®)</strong></td>
<td>33,8</td>
<td>8,9</td>
<td><strong>VEGFR 1-3; PDGFR β; c-KIT, RET, RAF</strong></td>
</tr>
<tr>
<td><strong>Sunitinib (Sutent®)</strong></td>
<td>18,9</td>
<td>5,5</td>
<td><strong>VEGFR 1-3; PDGFR β; c-KIT, RET, Flt3; CSF-1R</strong></td>
</tr>
<tr>
<td><strong>Axitinib (Inlyta ®)</strong></td>
<td>29,2</td>
<td>9,6</td>
<td><strong>VEGFR 1-3; PDGFR α-β; c-KIT</strong></td>
</tr>
<tr>
<td><strong>Vemurafenib (Zelboraf®)</strong></td>
<td>7-23</td>
<td>2</td>
<td><strong>BRAF</strong></td>
</tr>
<tr>
<td><strong>Pazopanib (Votrient®)</strong></td>
<td>4,5</td>
<td>1,8</td>
<td><strong>VEGFR 1-3; PDGFR α-β; c-KIT; RAF</strong></td>
</tr>
</tbody>
</table>

Balagula Y. The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: a systematic review of literature and meta-analysis. *Invest New Drugs, 2011.*

Belum VR. The risk of hand foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Invest New Drugs, 2013.*

Fischer A. The risk of hand foot skin reaction to axitinib, a novel VEGF inhibitor: a systematic review of literature and meta-analysis. *Invest New Drugs, 2013.*
Hand foot syndrome – key points

- **Chemotherapy and hand foot syndrome**: symmetric diffuse erythema, inflammation, edema, blistering. **Palms** more than soles. Capecitabine and liposomal doxorubicin.

- **Targeted therapies and hand foot skin reaction**: pressure-bearing areas (lateral aspect of the feet, heels, fingertips, interphalangeal joints...). **Localized** hyperkeratotic lesions, perilesional halo. **Soles** more than palms. Multitargeted angiogenesis inhibitors and anti-BRAF monotherapy.

A 59-year-old man treated with platinum-based and fluorouracil chemotherapy in combination with anti-EGFR cetuximab, for a locally advanced Head and Neck carcinoma. He developed bilateral periungual lesions, with a purulent discharge.

What is the most likely diagnosis (choose the single best response):

1. Cetuximab toxic effect
2. Fluorouracil toxic effect
3. Cisplatin toxic effect
4. Paraneoplastic syndrome
A 59-year-old man treated with platinum-based and fluorouracil chemotherapy in combination with anti-EGFR cetuximab, for a locally advanced Head and Neck carcinoma. He developed bilateral periungual lesions, with a purulent discharge.

What is the most likely diagnosis (choose the single best response):

1. Cetuximab toxic effect
2. Fluorouracil toxic effect
3. Cisplatin toxic effect
4. Paraneoplastic syndrome
The Nail...

Damage to the nail folds: paronychia, periungual pyogenic granulomas
Targeted therapies, *paronychia* and *pyogenic granuloma*

**EGFR**¹ – **MEK** – **mTOR** inhibitors

afatinib, erlotinib, cetuximab, panitumumab, gefitinib, trametinib, selumetinib, everolimus, temsirolimus….

¹: All-grade nail toxicity overall incidence of EGFR inhibitors: 17.2% (95% CI: 13.8–21.3%, RR =77)

*Overgrowing of friable granulation tissue on lateral and/or proximal nail folds, mimicking ingrown nails*

Pyogenic granuloma – correct nail curvature!

Fig 7. Procedure for using tape to treat paronychia.

Liquid nitrogen, topical steroids/antibiotics in combination, silver nitrate.....
<table>
<thead>
<tr>
<th>Baseline</th>
<th>W2</th>
<th>W4</th>
</tr>
</thead>
</table>

*D'andrea M, Casassa E, Fabbrocini G, Sibaud V. Efficacy and safety of topical blocking agents in the management of targeted therapy-related pyogenic granuloma. Support Care Cancer, 2018 (in progress).*
Fissures – skin cracking

**EGFR / MEK inhibitors**

afatinib, erlotinib, cetuximab, panitumumab, gefitinib, trametinib, selumetinib, ....
Fissures – skin cracking

« Cyanoacrylate Liquidband » = « Superglue »
**EGFR/MEK inhibitors -Dermatological toxicities**

Papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to epidermal growth factor receptor inhibitors


**Onycholysis and chemotherapy**

* Taxanes *(docetaxel, paclitaxel) +++, doxorubicin, etoposide, capecitabine........*

Separation of the nail plate from the nail bed – results from toxic effects to the bed epithelium, leading to plate detachment.

43% and 35% all-grade incidence with paclitaxel (95% CI: 18-73,3%) and docetaxel (95% CI: 29,9-40,2%, RR 77,7), respectively.

Onycholysis management – supportive care

Preventive measures: repeated nail trimming, frozen gloves 1/socks

Curative measures: partial removal of the nail plate and nail bed cleaned and cultured – dose reduction

1: Nail changes decreased from 51% to 11% of hands wearing frozen gloves

**Grade 0***

*Asymptomatic separation of the nail bed from the nail plate or nail loss*

**Preventive nail care instructions given – frozen gloves should be considered**

Continue drug at current dose and monitor for change in severity

*If infection is suspected, apply topical antibiotics or antifungal agent*

Reassess after 2/3 weeks. If reaction worsens proceed to next step

**Grade 1***

**Grade 2***

*Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental activities of daily living (ADL)*

Continue drug at current dose and monitor for change in severity; obtain bacterial/viral/fungal cultures if infection is suspected;

*If infection, start oral antibiotics* with anti- *Staphylococcus aureus and Gram + coverage*

*If painful haematoma or subungual abscess is suspected, partial or total nail avulsion is required*

**Pain control**

Reassess after 2 weeks; if reactions worsen or do not improve Interrupt treatment until severity decreases to grade 0-1;

Interrupt treatment until severity decreases to grade 0-1; obtain bacterial/viral/fungal cultures if infection is suspected; and continue treatment of nail reaction with the following:

*If infection, start oral antibiotics* with anti- *Staphylococcus aureus and Gram + coverage*

*If painful haematoma or subungual abscess is suspected, partial or total nail avulsion is required*

**Pain control**

Reassess after 2 weeks; if reactions worsen or do not improve, please consider dose interruption or discontinuation per protocol and switch to another antineoplastic agent

---

Check Point Inhibitors - Safety prevalence

<table>
<thead>
<tr>
<th>Safety profile</th>
<th>Ipilimumab + nivolumab (1)</th>
<th>Nivolumab alone</th>
<th>Ipilimumab alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related adverse events</td>
<td>91 - 95%</td>
<td>82.4%</td>
<td>93%</td>
</tr>
<tr>
<td>grade 3/4 adverse events</td>
<td>54%</td>
<td>16.3%</td>
<td>24%</td>
</tr>
<tr>
<td>GI select adverse events (colitis, diarrhea)</td>
<td>51% (21% grade 3)</td>
<td>19.5%</td>
<td>37% (10.9% grade 3)</td>
</tr>
<tr>
<td>Hepatic select adverse events (hepatitis, transaminitis)</td>
<td>27.7%</td>
<td>6.4%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Pulmonary select adverse events</td>
<td>7-11.7%</td>
<td>1.6%</td>
<td>1.9-4.3%</td>
</tr>
<tr>
<td>Endocrine select adverse events (thyroid disorders, hypophysitis, adrenal insufficiency)</td>
<td>34%</td>
<td>14.4%</td>
<td>17%</td>
</tr>
<tr>
<td>Skin select adverse events (rash, pruritus, vitiligo)</td>
<td>59-71.3%</td>
<td>41.9%</td>
<td>58.7%</td>
</tr>
<tr>
<td>Treatment related AE leading to discontinuation (2)</td>
<td>36.4%</td>
<td>7.7%</td>
<td>14.8%</td>
</tr>
</tbody>
</table>

Anti-PD-1/PD-L1 and nonspecific maculopapular rash

- **Most prevalent** skin toxicity – *Calculated all-grade incidence*: 14.3% and 16.7% for nivolumab and pembrolizumab, respectively
- *Develops after first cycles - shorter time to onset* than other toxicities
- *Mainly located on trunk and extremities* – macules, papules, scaling - Pruritus+++

- *Aberrant targeting of self antigens into the dermis/epidermis by reactivated CD4+/CD8+ T cells?*

Anti-PD-1/PD-L1 and nonspecific *maculopapular rash*

- **Self limited** - Less than 2\% of grade 3 or higher
- Most relevant histopathological features: eczematiform pattern with *spongiotic dermatitis* and exocytosis
- **Early management** is required for limiting exacerbation of the lesions and treatment discontinuation (moderate to high-potency topical steroids, moisturizers, oral antihistamines...)
- A skin biopsy performed if *atypical* lesions or *persistent/recurrent/intolerable* grade 2 or grade 3
Anti-PD-1/PD-L1 and psoriasiform eruptions

- Incidence currently unknown
- Occurrence or exacerbation of a preexisting psoriasis

Anti-PD-1/PD-L1 and vitiligo

- Associated *hair depigmentation*

- Does not require specific treatment other than photoprotective measures - Usually *persists* beyond immunotherapy discontinuation

- *Surrogate marker for treatment response* (objective response or overall survival)


Hair toxicities

- Uncommon toxicities (<2%)

- Alopecia areata (ipilimumab) – progressive hair repigmentation
Universalis-type

**Nail toxicities**

- **Uncommon toxicities (<2%)** – not published – histopathological findings not available

- **Psoriasis, lichenoid reactions. Paronychia, onycholysis, Brittle nails?**

Oral lichenoid reactions

- *reticulated white streaks* consistent with Wickham’s striae
- Papular, plaque-like, ulcerative or atrophic/erythematous lesions
- *either isolated* or associated with skin or genital involvement
Grade 1
Macules/papules covering <10% BSA with or without symptoms (e.g. pruritus, burning, tightness)

Symptomatic management:
Continue anti-PD-1/PD-L1 antibodies
Reassess after 2 weeks and monitor for change in severity

Grade 2*
Macules/papules covering 10%-30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental activities of daily living (ADL)

Symptomatic management:
Continue anti-PD-1/PD-L1 antibodies, reassess after 1-2 weeks and monitor for change in severity:
- If persistent (or intolerable grade 2), delay immunotherapy and consider oral corticosteroids (0.5-1 mg/kg/day). Once improved, taper steroids over 1 month and resume immunotherapy when systemic steroid dose is < 10 mg prednisone equivalent
- If worsened, manage as grade 3

*: A skin biopsy should be performed in the case of atypical lesions, persistent grade 2 and grade 3 or life-threatening skin reactions

Grade 3*
Macules/papules covering >30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting self-care ADL

Symptomatic management: topical moisturizers (if tolerated), high or very high-potency topical steroids (e.g. clobetasol), oral antihistamines, oral steroids (1mg/kg/day)

Delay immunotherapy, reassess after several days and monitor for change in severity:
- If persistent or worsened: permanently discontinue immunotherapy and supportive measures
- If improved to grade 1: taper steroids over 1 month and resume immunotherapy when systemic steroid dose is < 10 mg prednisone equivalent - close follow-up

Life-threatening reactions*
(blisters and exfoliative rash, fever, mucosal ulcerations, facial oedema, Nikolsky sign, etc.)

Permanently discontinue - supportive measures

Symptomatic Management:
- Topical moisturizers applied to full body surface (if tolerated),
- Topical steroids applied to affected areas,
- Oral antihistamines

DERMATOLOGY
AND ANTICANCER THERAPIES
Practical Handbook

sibaud.vincent@iuct-oncopole.fr