EGFR inhibitors

Monoclonal antibodies
- Cetuximab (Erbitux®)
- Panitumumab ( Vectibix®)

Oral tyrosine kinase inhibitors
- Erlotinib (Tarceva®)
- Gefitinib (Iressa®)
- Lapatinib (Tyverb®)
- Afatinib (Giotrif®)

EGFR is abundantly expressed in the skin


EGFR inhibitor skin toxicity

Acneiform eruption
Xerosis, eczema, fissures
Nail changes
Hair changes
Hyperpigmentation
Telangiectasia
Mucosal changes


Cutaneous side effects of EGFR-inhibitors and their management

Siegfried Segaert
Dermatology Dept
University Hospital Leuven
Belgium

4th BADO meeting
Brussels, January 14th 2017
Acneiform eruption: grade 1

Acneiform eruption: grade 2

Acneiform eruption: grade 3

Xerosis, eczema, fissures
Nail changes

Hair changes

Hyperpigmentation

Telangiectasia

Mucosal changes

Radiation and cetuximab combination therapy
Sparing of previously irradiated skin

Acneiform eruption by MEK-inhibitor

Transgenic mice mimic EGFRi skin toxicity

Overall survival depends on severity of skin toxicity

EGFRi skin toxicity drastically impairs quality of life

Supportive treatment makes the difference!
Role of oral tetracyclines

Prophylactic minocycline 100 mg qd: Study design


Minocycline 100 mg qd + topical tazarotene 0.05% bid
on one side of face

Placebo + topical tazarotene 0.05% bid on one side of face


Prophylactic minocycline for acneiform eruption

Study design


Prophylactic treatment of acneiform eruption

Tetracycline 500 mg bid


Prophylactic tetracycline does not diminish the severity of epidermal growth factor receptor (EGFR) inhibitor-induced rash: results from the North Central Cancer Treatment Group (Supplementary N03CB)

Support Care Cancer (2011) 19:1801–1807

Table 2: Rash incidence and severity

<table>
<thead>
<tr>
<th>Time point (week)</th>
<th>Patients with rash (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetracycline arm (n=33)</td>
<td>Placebo arm (n=32)</td>
</tr>
<tr>
<td>4 weeks (any)</td>
<td>27 (82)</td>
<td>24 (75)</td>
</tr>
<tr>
<td>4 weeks (grade 2 or &gt;10% surface area)</td>
<td>17 (52)</td>
<td>14 (44)</td>
</tr>
<tr>
<td>8 weeks (any)</td>
<td>32 (97)</td>
<td>38 (63)</td>
</tr>
<tr>
<td>16 weeks (grade 2 or &gt;10% surface area)</td>
<td>26 (79)</td>
<td>22 (69)</td>
</tr>
</tbody>
</table>

Preventing or treating anti-EGFR related skin rash with antibiotics?

Eusman Pettrell, Karen Borgenova, Sandro Barni

Patients were treated with panitumumab (6 mg/kg) Q2 W plus FOLFIRI or panitumumab (9 mg/kg) Q3W plus irinotecan (investigator’s choice).

**Phase 2 Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial: prophylactic vs. reactive skin treatment in 2nd-line treatment of metastatic CRC**

- **Prophylactic skin treatment regimen:** skin moisturiser (daily); topical steroid (hydrocortisone 1% daily); doxycycline (100 mg BID); SPF ≥ 15 sunscreen before going outdoors.

**STEPP trial: incidence and time to first occurrence of grade ≥ 2 skin toxicities**

- **Parameters:**
  - Prophylactic (n=48)
  - Reactive (n=47)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prophylactic (n=48)</th>
<th>Reactive (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with grade ≥ 2 skin toxicity, n (%)</td>
<td>14 (29)</td>
<td>29 (62)</td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>11 (23)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>3 (6)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Median time to first event, weeks (95% CI)</td>
<td>NR</td>
<td>2.1 (1.1−4.3)</td>
</tr>
</tbody>
</table>

**Cetuximab-induced skin exanthema: prophylactic and reactive skin therapy are equally effective**

- **Prophylactic skin protocol**
  - grade 0: daily topical treatment: vitamin K1 (100kU), minocycline (2 x 100mg)
  - grade 1: cleaning cream, topical metronidazole
  - grade II: oral minocycline (40mg/day), topical metronidazole
  - grade III: oral minocycline (60mg/day), topical metronidazole

- **Reactive skin protocol**
  - no specific therapy

**Pan Canadian Rash Trial: A Randomised Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor-Induced Skin Toxicities in Patients With Metastatic Lung Cancer**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1, prophylactic treatment</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Arm 2, treatment at rash initiation</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Arm 3, treatment at grade 2 rash initiation only</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Total</td>
<td>84 (150)</td>
</tr>
</tbody>
</table>

**Antibiotic prophylaxis for skin toxicity induced by anti-epidermal growth factor receptor agents: a systematic review and meta-analysis**

- **A No treatment
  - B Reactive
  - C Prophylactic

**Any rash**
EGFR inhibitor skin toxicity treatment scheme

<table>
<thead>
<tr>
<th>Type of skin toxicity</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General measures: sun protection, lukewarm water, bath/shower oil for hygiene, emollients on hands and limbs</td>
<td></td>
</tr>
<tr>
<td>Acneiform eruption</td>
<td></td>
</tr>
<tr>
<td>Mild: metronidazole cream bid ± vitamin K1 cream</td>
<td></td>
</tr>
<tr>
<td>Moderate: metronidazole cream bid ± vitamin K1 cream, minocycline 100 mg qd</td>
<td></td>
</tr>
<tr>
<td>Severe: saline compresses 15 minutes bid, metronidazole cream up to 5 times daily, minocycline 300 mg qd, topical steroid (fluticasone propionate cream), bid cetirizine 10 mg qd for itch, bid oral/rewax 300 mg bid for S. aureus superinfection</td>
<td></td>
</tr>
<tr>
<td>Xerosis</td>
<td>Emollients, weak topical corticosteroids</td>
</tr>
<tr>
<td>Eczema</td>
<td>Propyleneglycol 50% in water 30 minutes under occlusion qd, salicylic acid 10% ointment qd</td>
</tr>
<tr>
<td>Fissures</td>
<td>Emollients, weak topical corticosteroids, antiseptic</td>
</tr>
</tbody>
</table>

EGFR inhibitors: papulopustular eruption

GRADE 1 (mild)

Mild eruption
No symptoms
No impact on ADL

TREATMENT
- Topical:
  - Metronidazole cream 1/d
  - Rozex® cream or emulsion, Rosacea, Nidazea®

- Systemic:
  - Tetracycline antibiotics
    - minocycline 1x100mg/d
    - lymecycline 1x300mg/d
  - or
  - postpone to grade 2

GRADE 2 (moderate)

Moderate eruption
Some symptoms mainly itch
Minor impact on ADL*

TREATMENT
- Topical:
  - Metronidazole cream 1/d
  - Rozex® cream or emulsion, Rosacea, Nidazea®
- Corticoid: mild or moderate potent

- Systemic:
  - Tetracycline antibiotics
    - minocycline 1 to 2x100mg/d
    - lymecycline 1 to 2x300mg/d

- Symptomatic:
  - Antihistamines (older antihistamines stronger itch reducing effect but more sedation)

Re-evaluate after 2 weeks – if not better refer to dermatologist

GRADE 3 (severe)

Severe eruption
Severe symptoms
Major impact on ADL*

TREATMENT
- Refer to dermatologist
- Topical:
  - Corticoid: moderate potent

- Systemic:
  - Tetracycline antibiotics
    - minocycline 2x100mg/d
    - lymecycline 2x300mg/d
  - or
  - isotretinoin 20-30mg/d

- Symptomatic:
  - Antihistamines (older antihistamines stronger itch reducing effect but more sedation)

If not responding to therapy consider dose delay
After 2 weeks treatment:
- minocycline 2 x 100 mg/d
- saline compresses
- metronidazole 2% cream

After 1 week treatment:
- cefuroxim axetil 2 x 500 mg (5 d)
- topical fluticasonepropionate cream

After 2 weeks treatment:
- minocycline 100 mg/d
- metronidazole 2% cream
- cefuroxim axetil 2 x 500 mg (5 d)
After 1 week treatment:
- propylene glycol/water
- salicylic acid 10% in petrolatum

Thank you for your kind attention