TARGETED THERAPIES AND THEIR CUTANEOUS TOXICITIES

Brussels, 14/1/2017

Multikinase inhibitors:
- Regorafenib (Stivarga®; VEGFR1-3, (B)RAF, PDGFRβ, c-KIT)
- Sorafenib (Nexavar®; RAF, VEGFR2-3, PDGFRβ, FLT3)
- Sunitinib (Sutent®; c-KIT, VEGFR2, PDGFRβ, FLT3)
- Imatinib (Gleevec®, c-KIT, BCR-ABL, PDGFRβ)
- Avitaxib, Inifnetib, Pazopanib

Regorafenib skin toxicity

Regorafen: AEs in previously-treated mCRC
- The most common (≥10%) drug-related, treatment-emergent AEs of any grade experienced by patients enrolled in CORRECT1

<table>
<thead>
<tr>
<th>Treatment-related adverse event, %</th>
<th>Regorafenib + BSC (n=500)</th>
<th>Placebo + BSC (n=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hand−foot skin reaction</td>
<td>47% 17% 0 8% &lt;1% 0</td>
<td>30% 10% 0 5% 1% 0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47% 9% &lt;1% 12% 5% &lt;1%</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34% 5% &lt;1% 8% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29% 3% 0 15% 3% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Voice changes</td>
<td>29% &lt;1% 0 8% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28% 3% 0 6% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>27% 5% 0 6% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26% 5% 0 6% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25% &lt;1% 0 8% 2% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14% 2% 0 5% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>14% &lt;1% 0 11% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>14% 2% 0 5% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13% 2% &lt;1% 2% 1% 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
<tr>
<td>Fever</td>
<td>10% 1% 0 3% 0 0</td>
<td>4% 1% 0 &lt;1% 0 0</td>
</tr>
</tbody>
</table>

Hand-Foot Skin Reaction (HFSR)

- HFSR is distinct from the more widely known hand-foot syndrome (HFS also known as PPE, palmar-plantar erythrodysesthesia) which occurs with older therapies such as capecitabine.
- Cutaneous areas typically affected by HFSR are those under the most pressure or friction, such as the palms of the hand, soles of the feet, fingers or toes.
- HFSR typically develops soon (2-4 weeks) after a patient starts treatment.
- HFSR is not life-threatening and usually resolves with appropriate management and/or dose modification.


HFSR: clinical presentation

- HFSR is characterized by lesions localized to frictional and weight-bearing areas of the skin (heels, metatarsal heads,...).
- Initially, affected areas become tender and erythematous.
- Lesions become edematous and evolve into painful blisters.
- Blister transformation into painful calluses (thickening of the epidermis) affecting the patient’s ability to perform daily activities.


Hand-foot skin reaction

Grade 1

Grade 2

Hand-foot skin reaction

Grade 1

Grade 2
HFSR: symptoms

- HFSR symptoms may include:
- Tenderness
- Dysesthesia and paresthesia (numbness – feeling of pins and needles)
- Pain
- Intolerance to contact with hot objects often precedes or accompanies HFSR


Hand-foot skin reaction: clinical picture

<table>
<thead>
<tr>
<th>Hand-foot skin reaction</th>
<th>Hand-foot syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions on friction/pressure points</td>
<td>Entire palms/soles</td>
</tr>
<tr>
<td>Onset after days to weeks</td>
<td>Onset after weeks to months</td>
</tr>
<tr>
<td>Painful blister → callus</td>
<td>Erythema, edema, scaling</td>
</tr>
<tr>
<td>Dysesthesia, pain</td>
<td>Dysesthesia, pain</td>
</tr>
<tr>
<td>Regorafenib, sorafenib, sunitinib, vemurafenib, dabrafenib, axitinib, pazopanib</td>
<td>5-FU, capecitabine</td>
</tr>
<tr>
<td>Insufficient repair of frictional skin trauma due to inhibition VEGFR + PDGFR</td>
<td>Concentration of cytostatic in skin via eccrine sweat ducts</td>
</tr>
</tbody>
</table>

Hand-foot skin reaction: histopathology

- Repetitive frictional trauma on thick epidermis of palms and soles
- Repair mechanisms fail due to inhibition of VEGFR and PDGFR
- Keratinocyte necrosis → spongiosis (intraepidermal edema) → blister formation
- Intensive inflammation
- Hyperproliferation of epidermal keratinocytes
- Hyperkeratosis and callus formation

Hand-foot skin reaction: pathophysiology

- Insufficient repair of frictional skin trauma due to inhibition of VEGFR and PDGFR

Early Skin Toxicity as a Predictive Factor for Tumor Control in Hepatocellular Carcinoma Patients Treated with Sorafenib
Hand-foot skin reaction: treatment

- Preventive measures:
  - remove calluses before starting treatment
  - avoid friction, pressure, irritation
  - nicely fitting shoes (no sandals or slippers) / cotton socks
  - wear gloves for washing, cleaning, working
  - don’t wash hands too often and avoid very hot water
  - use wash oil e.g. Eucerin wash oil
  - use hand- or foot cream
    - hand cream: Neutrogena, Huizinga Fagron, Eucerin hand cream
    - foot cream: Xerial feet, Eucerin foot cream
  - pressure absorbing silicone shoe sole

- Ultrapotent topical steroids for inflammation (redness, blisters)
  - e.g. Dermovate, preparation with salicylic acid + clobetasolpropionate

- Urea or salicylic acid ointment for hyperkeratosis (callus)
  - e.g. Xerial 10 (feet), Xerial 50

- Topical anaesthetics for pain
  - e.g. Xylocain gel

- Oral analgetics for pain if insufficient

- When the lesions are wet, take a swab and use oral antibiotics (adjust according to antibiogram) e.g. fleroxacin, cefuroxim

HFSR management: dose modifications

GRADE 1  GRADE 2  GRADE 3

First Occurrence
- Consider decreasing dose by 1 dose level and include mitigation support measures. Treatment reduction should be at least grade 2. When decreasing dose, reduce by 1 dose level. If dose reduction is permitted at the discretion of the treating physician.
- Treatment interruption will be made in Grade 1.
- When increasing treatment, treat at reduced dose level.
- Do not increase dose level within the same treatment cycle.
- A dose increase is permitted at the discretion of the treating physician.

Second Occurrence
- Discontinue treatment, decrease dose by 1 dose level.
- A dose reescalation is permitted at the discretion of the treating physician.

Third Occurrence
- Discontinue treatment.
- A dose reescalation is permitted at the discretion of the treating physician.

Fourth Occurrence
- Discontinue treatment permanently.

Maculopapular rash

- Skin rash may occur in patients treated with kinase inhibitors, including regorafenib
  - 26% of patients enrolled in CORRECT who were treated with regorafenib experienced skin rash or desquamation (all grades), compared with 4% of patients treated with placebo

- Symptoms associated with skin rash may include:
  - Erythematous macules or papules, suddenly appearing in a symmetrical way
  - Itch
  - Rarely pain, blisters, mucosal involvement in severe cases


Rash over time

**Maculopapular rash**

- Oral antihistamine for itch
  - e.g. loratadine daytime, hydroxyzine evening

- Anti-itch cream
  - e.g. menthol cream

- Potent topical steroid for moderate to severe rashes
  - e.g. clobetasolpropionate cream (Dermovate®)

- Oral steroids

Dose modification / interruption may be required for severe rash

Retreatment is possible except for Stevens-Johnson syndrome, TEN or DRESS

Alarm symptoms: pain, blisters, facial swelling, mucosal erosions

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**Stomatitis**

- Common (27%)
- 5-14 days after start
- Risk factors: old age, poor dental hygiene, poor nutritional status
- Preventive measures:
  - dental care
  - mouth wash
  - avoid hot or spicy food
- Treatment
  - mouthwash containing saline ± antiseptic ± antifungal ± anaesthetic

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**Hair changes**

- Mild alopecia
- Depigmentation
- Curly hair

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**Eruptive naevi**


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**Regorafenib skin toxicity**

- Hand-foot skin reaction (50%)
- Alopecia (30%), depigmentation of hair, curly hair
- Maculopapular rash (25%)
- Stomatitis (25%)
- Seborrheic dermatitis-like rash face and scalp
- Eruptive naevi
- Keratoacanthoma

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**Skin toxicity of other MKIs:**

- Sorafenib
- Sunitinib
- Imatinib

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Sorafenib skin toxicity

- Hand-foot skin reaction (35% - 70%)
- Seborrheic dermatitis-like rash face and scalp (65%)
- Maculopapular rash (20-35%)
- Alopecia, curly hair
- Stomatitis (20%)
- Xerosis, itch (esp. scalp), eczema


Sorafenib skin toxicity

- Subungual splinter haemorrhages (30%)
- Keratosis pilaris-like follicular hyperkeratosis (20%)
- Inflamed seborrheic keratosis (10%)
- Keratinocyte neoplasia (keratosis, keratoacanthoma, SCC) (5%)
- Enulsive naevi (1%)
- Radiation recall dermatitis


Sorafenib: subungual splinter haemorrhages

Sorafenib: keratinocyte neoplasia

Sorafenib: keratosis pilaris-like follicular hyperkeratosis

Sunitinib skin toxicity

- Hand-foot skin reaction
- Stomatitis
- Facial / periorbital edema
- Yellow discoloration of the (facial) skin
- Hair depigmentation
- Subungual splinter haemorrhages
- Seborrheic dermatitis-like rash face and scalp (acneiform eruption?)
- Xerosis, itch (esp. scalp), eczema
- Genital and scrotal irritation

Imatinib skin toxicity

Edema (eyelid, facial to generalized)

Pigmentary changes
- localized or general depigmentation (esp. dark skin)
- hyperpigmentation (4%)
- repigmentation of grey hair (7%)

Rash (including AGEP, erythroderma, pityriasis rosea-like)

Pruritus

Xerosis