Mechanisms and Management of Diarrhoea from Anti-VEGFR-TKIs

Manuela Schmidinger
Medical University of Vienna
Austria
Clinical Presentation

- Frequency and severity varies between patients
- Intensity is dose-dependent
- According to patients, grade 3 diarrhoea often develops:
  1. first with an increased frequency and loose stool
  2. followed by pale stool
  3. followed by watery fatty stools (> 7 stools/d, grade 3)

- Frequency increases with fat intake
- TKI interruption: normalization within few days
Etiology of VEGFR-TKI-Diarrhoea?

According to the clinical presentation:

• TKI’s appear to induce changes in
  – the bowel function (frequency…)
  – the exocrine pancreas function (fatty pale stool, dependent on fat intake)
Understanding The Underlying Pathomechanism

- Would require stool analyses of patients with diarrhoea under TKI treatment and biopsies

- What is known? (PubMed)

- Stool analysis: 58 163
- Stool analysis AND VEGFR-tyrosine kinase inhibitor: 2
- These 2 focus on pharmacokinetics, distribution and metabolism
Current Knowledge???

- We don’t know at all why VEGF(R)-TKIs induce diarrhoea
- We only could observe that when compared to multikinase-inhibitors\(^1\)\(^-\)\(^5\), pure VEGF-inhibitors do NOT induce diarrhoea when used as monotherapy\(^6\)

<table>
<thead>
<tr>
<th></th>
<th>SUN(^1)</th>
<th>SOR(^2)</th>
<th>PAZ(^3)</th>
<th>AX(^2)</th>
<th>TIVO(^4)</th>
<th>CABO(^5)</th>
<th>BEV(^6) mono</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>53</td>
<td>53</td>
<td>52</td>
<td>55</td>
<td>18</td>
<td>50</td>
<td>nr</td>
</tr>
<tr>
<td>Grades ≥3</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Such Differences have Created New Toxicity Definitions

- **On-target toxicities**: due to VEGF-inhibition
  - induced by pure VEGF-inhibitors such as bevacizumab
  - include hypertension, wound-healing disorders, proteinuria

- **Off-target toxicities**: due to PDGFR, KIT, FLT3 etc inhibition
  - induced by multikinase-inhibitors such as sun, sor, paz, ax...
  - occur in addition to VEGF-associated toxicities
  - include myelotoxicity, HFS...diarrhoea?
Is Diarrhoea an Off-Target Toxicity?

...related to PDGFR, c-KIT etc. inhibition rather than VEGF-inhibition...
If Diarrhoea was an Off-Target Toxicity, then Agents with „Weak“ Off-Target Inhibition Should Be Safe...
Sorafenib is an Example for a „Weak“ Off-Target-Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>VEGFR-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>PDGFR-α</th>
<th>PDGFR-β</th>
<th>c-kit</th>
<th>Flt-3</th>
<th>RET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib¹</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>73</td>
<td>215</td>
<td>48</td>
<td>619</td>
<td>232</td>
</tr>
<tr>
<td>Sorafenib¹</td>
<td>9</td>
<td>28</td>
<td>7</td>
<td>933</td>
<td>1129</td>
<td>1862</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib¹</td>
<td>21</td>
<td>34</td>
<td>3</td>
<td>143</td>
<td>75</td>
<td>40</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Axitinib²</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>N/R</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>N/R</td>
</tr>
<tr>
<td>Tivozanib³</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>N/R</td>
<td>1.7</td>
<td>1.6</td>
<td>422</td>
<td>N/R</td>
</tr>
</tbody>
</table>

2. Escudier & Gore. Drugs R D 2011; 11: 113–126
Axitinib is a Strong Off-Target Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>VEGFR-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>PDGFR-α</th>
<th>PDGFR-β</th>
<th>c-kit</th>
<th>Flt-3</th>
<th>RET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib(^1)</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>73</td>
<td>215</td>
<td>48</td>
<td>619</td>
<td>232</td>
</tr>
<tr>
<td>Sorafenib(^1)</td>
<td>9</td>
<td>28</td>
<td>7</td>
<td>933</td>
<td>1129</td>
<td>1862</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib(^1)</td>
<td>21</td>
<td>34</td>
<td>3</td>
<td>143</td>
<td>75</td>
<td>40</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Axitinib(^2)</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>N/R</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>N/R</td>
</tr>
<tr>
<td>Tivozanib(^3)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>N/R</td>
<td>1.7</td>
<td>1.6</td>
<td>422</td>
<td>N/R</td>
</tr>
</tbody>
</table>

2. Escudier & Gore. Drugs R D 2011; 11: 113–126
# Low Off-Target Inhibition Can’t Be Linked to Diarrhoea

## Inhibitory concentrations (kinase IC$_{50}$ [nM]) for relevant targets

<table>
<thead>
<tr>
<th></th>
<th>VEGFR-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>PDGFR-α</th>
<th>PDGFR-β</th>
<th>c-kit</th>
<th>Flt-3</th>
<th>RET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pazopanib</strong>$^1$</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>73</td>
<td>215</td>
<td>48</td>
<td>619</td>
<td>232</td>
</tr>
<tr>
<td><strong>Sorafenib</strong>$^1$</td>
<td>9</td>
<td>Diarrhoea</td>
<td>SOR$^2$</td>
<td>AX$^2$</td>
<td>1129</td>
<td>1862</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td><strong>Sunitinib</strong>$^1$</td>
<td>21</td>
<td>All grades</td>
<td>53</td>
<td>55</td>
<td>75</td>
<td>40</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td><strong>Grades &gt;3</strong></td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Axitinib</strong>$^2$</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1-0.3</td>
<td>N/R</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>N/R</td>
</tr>
<tr>
<td><strong>Tivozanib</strong>$^3$</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>N/R</td>
<td>1.7</td>
<td>1.6</td>
<td>422</td>
<td>N/R</td>
</tr>
</tbody>
</table>

2. Escudier & Gore. Drugs R D 2011; 11: 113–126
Two Quite Similar Agents in Terms of On AND Off-Target -Inhibition

<table>
<thead>
<tr>
<th></th>
<th>VEGFR-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>PDGFR-α</th>
<th>PDGFR-β</th>
<th>c-kit</th>
<th>Flt-3</th>
<th>RET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib¹</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>73</td>
<td>215</td>
<td>48</td>
<td>619</td>
<td>232</td>
</tr>
<tr>
<td>Sorafenib¹</td>
<td>9</td>
<td>28</td>
<td>7</td>
<td>933</td>
<td>1129</td>
<td>1862</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>Sunitinib¹</td>
<td>21</td>
<td>34</td>
<td>3</td>
<td>143</td>
<td>75</td>
<td>40</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>Axitinib²</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>N/R</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>N/R</td>
</tr>
<tr>
<td>Tivozanib³</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>N/R</td>
<td>1.7</td>
<td>1.6</td>
<td>422</td>
<td>N/R</td>
</tr>
</tbody>
</table>

2. Escudier & Gore. Drugs R D 2011; 11: 113–126
... Differ Considerably in Terms of Diarrhoea Incidence

<table>
<thead>
<tr>
<th></th>
<th>Inhibitory concentrations (kinase IC$_{50}$ [nM]) for relevant targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VEGFR-1</td>
</tr>
<tr>
<td>Pazopanib$^1$</td>
<td>7</td>
</tr>
<tr>
<td>Sorafenib$^1$</td>
<td>9</td>
</tr>
<tr>
<td>Sunitinib$^1$</td>
<td>21</td>
</tr>
<tr>
<td>Axitinib$^2$</td>
<td>0.1</td>
</tr>
<tr>
<td>Tivozanib$^3$</td>
<td>0.2</td>
</tr>
</tbody>
</table>

|                  | diarrhoea | AX$^2$ | TIVO$^4$ |
| All grades       | 55 | 18 |
| Grades >3        | 11 | 2 |

Currently Available Data on „On- and Off-Target Inhibition“

• Do NOT help to understand the pathomechanism of VEGFR-TKI associated diarrhoea
• → both weak (sorafenib) and stronger (axitinib) off-target inhibitors induce diarrhoea
• → even agents with similar „on- and off-target“ inhibition differ considerably regarding induction of diarrhoea (axitinib, tivozanib)
Diarrhoea and TKI-Treatment

• Nevertheless, it appears that the MoA of these agents is responsible for diarrhoea

• *Non-drug related causes can be ruled out in the majority of patients: occurrence strongly correlates with the treatment*

• Which target-inhibition could be responsible?
Diarrhoea Could Be The Result of...

1. Strong VEGF-inhibition
2. KIT-inhibition
3. ....???
Diarrhoea as a Result of Strong VEGF-Inhibition
Does VEGF Inhibition Affect Normal Tissue at All?

VEGF and VEGFRs:

- still highly expressed in adult organs including endocrine glands, intestine, lung, and kidney\(^1\)
- VEGF plays a role in maintaining parts of the normal adult vasculature\(^1\)

Addition of VEGF(R)-inhibitors significantly reduces the capillaries network in pancreatic islets and intestinal villi\(^2\)

---

These findings suggest that VEGF-Inhibition may impair the function of digestive organs such as intestines and pancreatic gland. Is diarrhoea a result of this?
VEGF-induced Changes in The **Bowel Mucosa** May Result in Diarrhoea

- In the intestinal mucosa, **even small perturbations of blood flow can lead** to rapid metabolic changes characteristic for **ischemia** and **hypoxia**\(^1\)
- Epithelial **hypoxia** is clinically **associated with diarrhoea**\(^2\)
- Bowel mucosa changes are consistent with **ischemic colitis**\(^3\)

**VEGF-induced Changes in the **Exocrine Pancreas** may Cause Diarrhoea**

- patients with strong VEGFR-inhibitor treatment frequently report on fatty stools

VEGFR-inhibitors were shown to
- decrease the zymogen granules in the pancreas
- reduce pancreatic islets capillaries

1. observed in animals unter axitinib (Axitinib investigator’s Broschure 2012).
Diarrhoea as a Result of KIT-Inhibition
KIT-Inhibition and Bowel Function

• KIT is expressed by interstitial cells of Cajal, the pacemaker cells of the intestine

• Cajal cells are adjacent to the nerve fibers of the myenteric plexus

• regulate rhythmic contractions in the muscle layer

• could potentially cause altered motility patterns and diarrhoea

• High expression of Kit in interstitial cells of the Cajal might be a potential mechanism for diarrhoea induced by imatinib or sunitinib

2. Deininger et al. 2003
Management of Diarrhoea from TKI’s
Impact of Dietary Measures on TKI-Induced Diarrhoea (1)

- E.g. grated oxidized apples
- Evidence or common knowledge?
- Both, however (published) evidence from randomized double-blinded trials\(^1\) only in children
- “significantly reduced stool frequency in the treatment group compared to the control group”

Impact of Loperamide on TKI-Induced Diarrhoea (2)

- **Loperamid**: slows transit by decreasing tone of the longitudinal smooths muscles and by increasing tone of circular smooths muscles of the intestinal wall\(^1\)
- Increases time substances stay in the intestines, allowing for more water to be absorbed\(^1\)
- Decreases colonic movements\(^1\)
- Suppresses gastrocolic reflux\(^1\)
- *However: patients with watery diarrhoea may report that a slower transit of watery stool is even worse*

1. Placidi E, Aliment Pharmacol Ther 2012
Impact of Pancrelipase on TKI-Induced Diarrhoea (3)

• In patients who complain on bowel movements during meals or right after, we should consider pancreatic insufficiency
• Addition of *pancreatin might be helpful: treatment plan: 5 meals per day, 25 000 U pancreatin with each meal*
• Do we have a proof for pancreatic insufficiency in sunitinib-patients? → NO
  – Pancreatic atrophy sometimes observed on CT scans in patients with mRCC and sunitinib
  – atrophy might be present long before signs on CTs
  – before Pancreatic *Elastase* (PE) for assessment of exocrine pancreatic function is abnormal
Patient FS, Sunitinib for mRCC

- Diarrhoea grade 3 despite grated apples and loperamide
- Bowel movements during meals or right after
- Addition of pancreatin 5 meals per day, 25 000 U pancreatin with each meal
- Reduction of diarrhoea from grade 3 to 1
- Full-dose first-line TKI treatment maintained: PFS 28+ months
Impact of Probiotics on TKI-Induced Diarrhoea (4)

• Probiotics
• have been shown to prevent diarrhea in inflammatory bowel disease
• Preclinical data yielded a similar efficacy in CID\textsuperscript{1,2}
• Clinical setting, a combination of Lactobacillus rhamnosus and fiber resulted in a significant reduction of grade 3/4 diarrhea (37 versus 22%) in a randomized study in patients with colorectal cancer and chemotherapy\textsuperscript{3}
• Individual sunitinib-patients report on considerable benefits from probiotics

Impact of Other Measures (5)

- **Budesonide**: topical corticosteroid
- **Benefits shown in patients with CID**
  - reduces inflammation in the bowel
  - reduction of CID from 4.2 to 1.8 days together with loperamide\(^1\)
- In loperamide-refractory patients: reduction of CID grade in > 50% of the patients treated with irinotecan or 5-FU\(^2\)
- **No data in TKI-patients**

Impact of Other Measures (6)

• **Long-acting formulation of octreotide**, synthetic somatostatin
  MoA:
  – decreased secretion of vasoactive intestinal peptide (VIP);
  – prolongation of intestinal transit time
  – reduced secretion and increased absorption of fluid and electrolytes

• FDA-approved for the treatment of diarrhea related to VIP-secreting tumors and symptoms due to carcinoid syndrome

• However: no difference to placebo in patients with colorectal cancer receiving 5-FU based chemoradiation¹

• **No data in TKI-patients**

1.Zachariah B et al., J Natl Cancer Inst 2010
Conclusions

- So far no clear understanding of the pathomechanism behind VEGFR-TKI-induced diarrhoea
- Could be achieved by biopsy of intestinal mucosa and stool analyses
- It is completely unclear if diarrhoea is an on-target or off-target toxicity or both
- Agents with similar MoA and IC-50 results (axitinib, tivozanib) differ regarding the incidence of diarrhoea: due to different pharmacokinetic, bioavailability, drug exposure etc.?
- Currently available strategies to prevent or treat diarrhoea include dietary measures, loperamide, pancrelipase, probiotics: benefits varies between patient