Mechanisms and Management of Diarrhoea from Anti-VEGFR-TKIs

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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]

	SUN[1]	SOR[2]	PAZ[3]	AX[2]	TIVO[4]	CABO[5]	BEV[6] mono
All grades	53	53	52	55	18	50	nr
Grades ≥3	5	7	3	11	2	7	0

1.Motzer RJ et al., New Engl J Med 2007; 2.Rini BI et al., Lancet 2011; 3.Sternberg C et al., J Clin Oncol 2010;
4.Eisen T et al., ESMO 2012; 5.Kurzrock R et al., J Clin Oncol 2011; 6.Bukowski RM et al, J Clin Oncol 2007

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

	Inhibitory concentrations (kinase IC_{50} [nM]) for relevant targets							
	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR-α	PDGFR-β	c-kit	Flt-3	RET
Pazopanib[1]	7	15	2	73	215	48	619	232
Sorafenib[1]	9	28	7	933	1129	1862	45	2
Sunitinib[1]	21	34	3	143	75	40	4	37
Axitinib[2]	0.1	0.2	0.1–0.3	N/R	1.6	1.7	>1000	N/R
Tivozanib[3]	0.2	0.2	0.2	N/R	1.7	1.6	422	N/R

1. Kumar *et al. Br J Cancer* 2009; 101: 1717–1723
2. Escudier & Gore. *Drugs R D* 2011; 11: 113–126
3. Gupta & Fishman. *Exp Opin Pharmacother* 2011; 12: 2915–2922

Axitinib is a Strong Off-Target Inhibitor

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Low Off-Target Inhibition Can't Be Linked to Diarrhoea

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Diarrhoea	SOR[2]	AX[2]
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Two Quite Similar Agents in Terms of On AND Off-Target -Inhibition

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… Differ Considerably in Terms of Diarrhoea Incidence

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diarrhoea	AX[2]	TIVO[4]
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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…

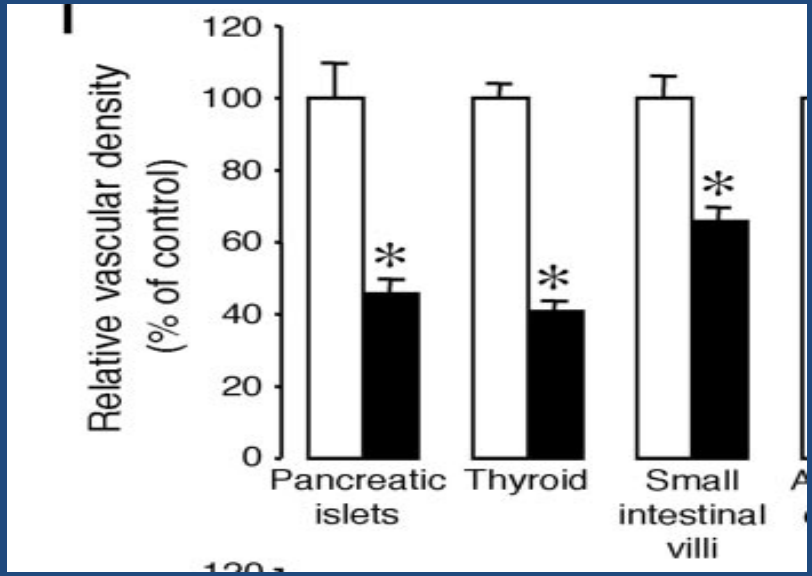
1. Strong VEGF-inhibition
2. KIT-inhibition
3. ….???

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]

1. Fan L and Iseki S *Arch Histol Cytol* 61: 17–28, 1998;
2. Tomomi Kamba *Am J Physiol Heart Circ Physiol 290: H560–H576, 2006*

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]

1.Wen Zheng The Faseb Journal 2009. 2. Sreenarasimhaiah J et al., Curr Gastroenterol 2005.
3.Lordick F et al., Int J Radiat Oncol Biol Phys 2006

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[1]
- reduce pancreatic islets capillaries[2]

1. observed in animals unter axitinib (Axitinib investigator‘s Broschure 2012).
2. Tomomi Kamba *Am J Physiol Heart Circ Physiol 290: H560–H576, 2006.*

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[1]
- 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]

1.Sanders K, Koh S, Ward S (2006).. *Annu Rev Physiol* **68**: 307–343
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”*

1.Becker B, Arzneimttelforschung 2006

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 insufficieny
- 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[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*[3]
- Individual sunitinib-patients report on considerable benefits from probiotics

1.Von Bultzingslowen I et al., Oral Microbiol Immunol 2003; Bowen JM Cancer Biol Ther 2007; 3. Osterlund P et al Br J **Cancer**. 2007

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 trated with irinotecan or 5-FU[2]
- No data in TKI-patients

1.Karthaus M et al., Oncology 2005; Lenfers BH et alAnn Oncol 1999

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 chemoradiation[1]
- No data in TKI-patients

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

Conclusions

- So far no clear undestanding of the pathomechanism behind VEGFR-TKI-induced diarrhoea
- Could be achieved by biopsy of intestinal mucosa and stool analyses
- It is completely unclear if diarhoea 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