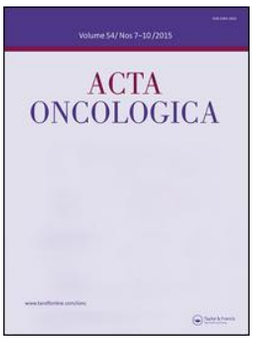

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Endoscopy in patients with diarrhea during treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors: Is the cause in the mucosa?

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ABSTRACT

Background Diarrhea is a frequently occurring adverse event during treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) and is mostly accompanied by abdominal cramps, flatulence and pyrosis. These complaints impair quality of life and lead to dose reductions and treatment interruptions. It is hypothesized that the diarrhea might be due to ischemia in bowel mucosa or inflammation, but the exact underlying pathophysiological mechanism of the diarrhea is still unknown. We aimed at exploring the mechanism for diarrhea in these patients by thorough endoscopic and histological assessment.

Materials and methods Endoscopies of the upper and lower gastrointestinal (GI) tract in 10 patients with metastatic renal cell carcinoma (mRCC) who developed diarrhea during treatment with VEGFR TKIs were performed.

Results Ten patients were included. The results showed endoscopically normal mucosa in the lower GI tract in seven patients without signs of ischemic colitis or inflammation. Gastroduodenoscopy revealed gastro-esophageal reflux disease, bulbitis and/or duodenitis with ulcers in eight patients. In three selected patients with bulbitis/duodenitis additional video capsule endoscopy was performed but revealed no additional intestinal abnormalities.

Conclusion We observed frequent mucosal abnormalities in the upper GI tract in VEGFR TKI-treated mRCC patients with diarrhea. Although these abnormalities provide insufficient explanation for the occurrence of diarrhea, we suggest to perform routine upper GI endoscopy in VEGFR TKI-treated patients with GI complaints.

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Tyrosine kinase inhibitors (TKIs) of the vascular endothelial growth factor receptors (VEGFR), such as sunitinib, sorafenib and pazopanib, have improved survival in patients with metastatic renal cell carcinoma (mRCC). These drugs showed to increase progression-free survival and stabilization of the disease compared to interferon alpha [1,2] or placebo [3,4]. VEGFR TKIs inhibit angiogenesis, cell proliferation and tumor cell invasion. In general, VEGFR TKIs are tolerated reasonably well, but diarrhea is a frequently reported side effect [1,3–7] which may persist for a prolonged period of time. In 53% of 375 patients treated with sunitinib diarrhea was observed and in 5% of cases it was severe, defined as grade 3 diarrhea according to the common terminology criteria for adverse events (CTCAE) [1]. A phase III study with pazopanib reported similar percentages, 52% of patients having diarrhea which was severe diarrhea in 4% [4].

Diarrhea negatively influences the quality of life due to flatulence, cramps, urge and fecal incontinence. Furthermore, diarrhea can necessitate dose reductions or interruptions, potentially leading to less effectiveness of treatment. Therefore, it is of utmost importance to understand, treat and if possible prevent VEGFR TKI-induced diarrhea.

Despite its frequent occurrence, the etiology and pathophysiological mechanisms that lead to diarrhea in patients treated with VEGFR TKIs have not been clarified yet. Several potential causes for diarrhea in these patients have been previously suggested. VEGFR TKIs do not exclusively inhibit the vasculature of tumors, but also have their effect on the blood supply of healthy organs. Cases have been published in which ischemic colitis and perforation have been reported after treatment with bevacizumab and VEGFR TKIs [8–12]. Chronic low-grade ischemia can also occur and lead to chronic symptoms. We hypothesized that ischemic conditions in the bowel mucosa might lead to the diarrhea in patients treated with VEGFR TKIs. Second, it is known that angiogenesis is involved in the pathogenesis of inflammatory bowel diseases [13,14]. It may be that inflammation has a role in the pathogenesis of the diarrhea.

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In order to explore possible causes of diarrhea in patients who developed diarrhea during treatment with a VEGFR TKI, including intestinal ischemia and mucosal inflammation, we performed an endoscopy of the upper and lower gastrointestinal (GI) tract.

Material and methods

Ten consecutive patients on VEGFR TKI treatment for mRCC who developed diarrhea of any grade according to the CTCAE [15] were asked for participation in this study. Diarrhea was defined as the sudden deviation of normal bowel movements, with a higher frequency of bowel movements (at least three times a day), a larger quantity and feces containing more water than before. Patients with a known history of bowel diseases, such as inflammatory bowel disease, lactose intolerance or celiac disease, were excluded. Patients using laxatives on a regular basis were also excluded.

The medical ethical committee of our institute (no. 2011/151) approved this study. After providing written informed consent, a thorough history was taken, covering all aspects of diarrhea and accompanying GI complaints in relation to treatment with the VEGFR TKI. In all patients, both a sigmoidoscopy and gastroduodenoscopy were performed. At least two biopsies from stomach, duodenum and sigmoid each were taken on formalin and liquid nitrogen and stored at -20°C until analysis. In case of macroscopic abnormalities targeted additional biopsies were taken. A pathologist with expertise in GI diseases (IN) assessed all biopsies in a systematic way. In the context of the ''ischemic'' hypothesis, additional immunohistochemical stainings on stomach, duodenal and sigmoid biopsies for CD31 (marker for endothelial cells), D2-40 (marker for lymphatic endothelial cells) and VEGFR2 (the receptor that mediates almost all of the known cellular responses to VEGF) were done. Stainings for cytomegalovirus (CMV) and *Helicobacter pylori* were performed to rule out an infectious cause.

Results

Patients

Ten patients with metastatic clear cell RCC were enrolled between November 2011 and March 2013. Patient characteristics are described in Table I. Nine patients were treated before study entry with sunitinib for a median duration of 11 months. One patient was on treatment with cediranib 30 mg once daily in a phase I study since 62 months. The median duration of therapy before occurrence of the diarrhea was five months (range 1–14 months), including four patients complaining of diarrhea since the first cycle. Patients complained about frequent bowel movements, median 4–5 times a day, typically starting in the late afternoon or early after dinner and occurring within a short time interval, e.g. two or three times within 30 minutes (Table II). Seven patients also reported nocturnal bowel movements necessitating passing stools at night. Five patients reported fecal incontinence. In eight patients, the diarrhea was accompanied with abdominal cramps and/or flatulence. Patients did not report undigested food, blood or mucus in the stools, nor did they describe the typical findings of steatorrhoe (pale, greasy, voluminous stools). Seven patients used loperamide chronically to control their complaints. All patients changed their food and drinking habits in an attempt to diminish the complaints: milk products, fat and spicy food were banned from the menu, with variable results.

Endoscopy: Macroscopic findings

In half of the patients the sigmoidoscopy showed macroscopic abnormalities with swollen mucosa, a polyp in the rectum, impression from outside accompanied by an ulcer, teleangiectasias and diverticulosis all occurring once (Table III). With gastroduodenoscopy macroscopic abnormalities were found in eight of 10 patients (Table III). Five patients had gastroesophageal reflux disease (GERD) and four patients had endoscopic signs of bulbitis/duodenitis with ulcers. In one patient with a long history of heartburns and a family history of reflux esophagitis, a carcinoma in situ of the esophagus was found, which was treated subsequently by endoscopic mucosal resection.

Endoscopy: Microscopic findings

The microscopic findings of the biopsies in patients by sigmoidoscopy and gastroduodenoscopy are shown in Table III. Biopsies of the sigmoid showed abnormalities in three patients: a hyperplastic polyp, localization of RCC in the submucosa/lamina propria and aspecific abnormalities in architecture with focal bleeding. In three patients the staining for VEGFR2 showed an increase of VEGFR2 in the epithelium and subepithelium of the sigmoid.

In biopsies of stomach and duodenum, six cases of chronic inflammation were found (60%), three cases of active inflammation, intestinal metaplasia and angiodysplasia (30%) and two cases of proton pump inhibitor effect, reactive gastropathy and infection with *H. pylori* each (20%). Stainings for CMV, D2-40 and CD31 were normal in all patients.

Additional tests

When we found the mucosal abnormalities such as ulcers and erosions, in the duodenum and bulbus of four patients, we hypothesized that this might explain the diarrhea and subsequently, three patients underwent a video capsule endoscopy (VCE) in order to assess the entire small intestine.

In two patients small angiodysplasias, superficial erosive lesions and microscopic hemorrhages were observed in the entire small intestine. In one patient the lesions were mostly localized in the most distal part of the small intestine and also in the right-sided colon. No ulcers were observed. In the last patient only very few superficial erosions were seen.

Discussion

Diarrhea is a frequently occurring adverse event of treatment with VEGFR TKI, which could lead to dose interruptions or reductions and diminish quality of life. The endoscopies performed in our study showed no definitive evidence for

Table I. Patient characteristics.

Pt no.	TKI	Dosage (per day)	Age (year)	Sex	BMI	Months on treatment	Start of diarrhea (months on treatment)	Concomitant medication
1	Sunitinib	37.5 mg CDD	63	M	26.4	12	7	Amlodipine, loperamide
2	Sunitinib	37.5 mg CDD	59	F	24.1	36	3	Atenolol, levothyroxine, loperamide
3	Sunitinib	50 mg 4/2	47	M	26.4	17	7	Amlodipine, atenolol, lisinopril, loperamide, omeprazole
4	Sunitinib	37.5 mg CDD	58	M	23.9	11	7	Amlodipine, levothyroxine, lisinopril, loperamide, pantoprazole
5	Cediranib	30 mg CDD	66	M	25.0	62	14	Amlodipine, doxycyclin, levothyroxine, loperamide
6	Sunitinib	50 mg 4/2	61	M	27.4	7	1	Amlodipine, ASA, hydrochlorothiazide
7	Sunitinib	25 mg CDD	60	M	43.7	10	1	Amlodipine, atenolol
8	Sunitinib	37.5 mg CDD	65	M	28.1	10	7	ASA, furosemide, isosorbide mononitrate, lisinopril, loperamide, metformin, nebivolol, oxycodone, pantoprazole, simvastatin
9	Sunitinib	37.5 mg 4/2	61	M	28.1	26	1	ASA, atorvastatin, chlortalidone, clopidogrel, diazepam, isosorbide mononitrate, loperamide, losartan, metoprolol, pantoprazole
10	Sunitinib	37.5 mg CDD	50	M	25.7	9	1	None

ASA, acetylsalicylic acid; BMI, body mass index; CDD, continuous daily dosing; F, female; 4/2, four weeks on two weeks off; M, male; pt no., patient number; TKI, tyrosine kinase inhibitor.

Table II. Patients' complaints of diarrhea and other gastrointestinal adverse events.

Patient	Frequency per day	Diarrhea during the night	Cramps	Flatulence	Pyrosis
1	4–5	Y	N	Y	N
2	5–6	Y	N	Y	N
3	4	Y	Y	Y	Y
4	5–6	Y	Y	N	Y
5	3–4	N	N	Y	N
6	4	N	N	N	Y
7	2–4	N	N	N	N
8	5–6	Y	Y	Y	Y
9	>7	Y	Y	Y	Y
10	3	Y	Y	Y	Y

ischemia or inflammation as the cause of the diarrhea. Unexpectedly, we found focal mucosal abnormalities, such as erosions and ulcers in esophagus, stomach and duodenum, in the majority of patients.

Despite the high prevalence of the diarrhea in patients with VEGFR TKI and the negative consequences on quality of life, research focusing on the cause of this adverse effect is scarce. As far as we know, no other cross-sectional studies in which endoscopy was performed had been published before. Thus far, only a retrospective case series was published in which colonoscopy was performed in patients treated with bevacizumab, which showed bowel mucosa changes consistent with ischemic colitis. However, these patients had severe anal pain and bowel perforation [8].

The first hypothesis of ischemia is supported by preclinical research in mice by Kamba et al. [16] which showed that capillaries of healthy tissue in adult mice regressed in reaction to anti-VEGF therapy. After anti-VEGF therapy for 2–3 weeks, 20–46% of capillaries in the microvilli in the small intestine regressed. In our study, neither endoscopic evaluation showed macroscopic signs of ischemia, nor did (immune)histological examination. The results of this study also did not give any indication that inflammation is involved in the pathogenesis of diarrhea. Biopsies of the sigmoid were almost exclusively normal as well as the macroscopic pictures were. Histology of biopsies of the upper GI tract showed signs of focal chronic and acute inflammation. However, the VCE, performed in three patients, showed only limited and patchy abnormalities in the small intestine. As the predominantly occurrence of abnormalities is in the upper GI tract, this is not a plausible explanation for the diarrhea.

A study performed by Mir et al. did show that the diarrhea and hypophosphatemia which developed in eight patients treated with sorafenib was due to a pancreatic exocrine dysfunction [17]. Pancreatic exocrine dysfunction leads to malabsorption, as well as other disorders, such as celiac disease, lactose intolerance and short bowel syndrome. A malabsorption syndrome could explain the macrocytosis, vitamin B12 deficit [18,19] and weight loss despite a normal caloric intake which often develops in patients who are treated with VEGFR TKIs. As a result of the nature of this study, we were not able to investigate non-mucosal diseases, such as pancreatic exocrine dysfunction. This should be the scope of new studies.

In this study, five of 10 patients showed signs of GERD. In addition, one patient was diagnosed with a carcinoma in situ of the esophagus. Three patients used acetylsalicylic acid (ASA), which is a known risk factor for the development of gastric and esophageal mucosal injury [20]. However, two of these patients also used a proton pump inhibitor in combination with ASA to protect their mucosa for the detrimental effects. In this study, seven patients had a body mass index (BMI) above 25 (see Table I) and were thus overweight, which is also a known risk factor for GERD. However, one of the patients with a healthy weight suffered from GERD, whereas the patient with very severe obesity did not have any abnormalities. Four of the five patients with GERD were symptomatic and complained of pyrosis, which started since the initiation of treatment with the VEGFR TKI. Due to the non-prospective nature of our study, a causal relationship between the reflux disease and the use of VEGFR TKI could not be evaluated.

In conclusion, this study did not support an ischemic or inflammatory cause as the underlying pathophysiological mechanism for diarrhea in patients treated with VEGFR TKIs. However, as an unexpected result, we found mucosal abnormalities, such as erosions and ulcers in esophagus, stomach and duodenum, in the majority of patients. Based on these results, we recommend routine gastroduodenoscopy in patients treated with VEGFR TKIs who report gastrointestinal symptoms, in order to timely diagnose and treat these abnormalities.

Table III. Macro- and microscopic findings in patients.

Pt no.	Macroscopic findings			Microscopic findings		
Esophagus/ Stomach	Duodenum	Sigmoid	Esophagus/Stomach	Duodenum	Sigmoid	
1	Pale mucosa, bleeding easily	Multiple ulcers	Normal	Focal limited intestinal metaplasia	Limited acute non-specified inflammation	Normal
2	• Reflux esophagitis grade A • Swollen, hyperemic mucosa	• Ulcer • Red, swollen folds	Swollen mucosa	• Limited intestinal metaplasia • Active inflammation + • Chronic inflammation ++ • *H. pylori* +	• Angiodysplasia • Focal chronic inflammation	Limited abnormalities in architecture, focal bleeding and edema
3	Polypoid lesion in metaplastic epithelium of esophagus	Normal	Normal	• At least carcinoma in situ of esophagus • Stomach: angiodysplasia	Normal	Normal
4	Small hernia diafragmatica	Mild bulbitis	• Impression from outside • Ulcus	Reactive gastropathy	Normal	Localization of a carcinoma in submucosa/lamina propria, consistent with RCC
5	Normal	Normal	Normal	Limited chronic inflammation	Normal	Normal
6	Reflux esophagitis grade D	Normal	Normal	• Chronic inflammation ++ • Active inflammation with influx of lymphocytes, neutrophils and eosinophils • *H. pylori*+	Normal	Normal
7	Normal	Normal	Polyp in rectum	Normal	Normal	Hyperplastic polyp
8	Reflux esophagitis grade A	Teleangiectasias	Teleangiectasias	• PPI effect • Focal intestinal metaplasia • Chronic inflammation +	Angiodysplasia	Normal
9	Reflux esophagitis grade A	Erosive bulbitis/duodenitis with multiple erosions and ulcers	Diverticulosis	• Reactive gastropathy • PPI effect	Normal	Normal
10	Reflux esophagitis grade B	Normal	Normal	Limited chronic inflammation	Normal	Normal

PPI, proton pump inhibitor.

Declaration of interest

The authors report no conflicts of interest.

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