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CASE REPORT

Improved Control of Tyrosine Kinase Inhibitor-Induced Diarrhea with a Novel Chloride Channel Modulator: A Case Report

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ABSTRACT

Despite the efficacy of tyrosine kinase inhibitors (TKIs) across multiple cancers, side effects including treatment-related diarrhea can impede a patient's ability to reach therapeutic doses or stay on therapy. Below, we present the case of a 72-year-old patient with metastatic papillary renal cell carcinoma recurrent despite nephrectomy. Over the course of treatment, the patient received multiple different tyrosine kinase inhibitors with varying efficacy. Treatment with the TKI cabozantinib after failure of two prior TKIs resulted in a clinical response with shrinkage of his nodal metastatic disease. However, the severe treatment-related diarrhea refractory to conventional management required both dose holds and dose reductions of cabozantinib. Off-label administration of crofelemer, a novel FDA-approved antidiarrheal agent, successfully controlled the treatment-related diarrhea and allowed resumption and partial dose increase of cabozantinib. This case suggests that crofelemer could be a viable therapeutic strategy to address TKI-induced diarrhea.

Keywords: Crofelemer; Diarrhea; Renal cell carcinoma; Targeted therapy-induced diarrhea; Tyrosine kinase inhibitor

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Key Summary Points

Why carry out this study?

In cancer patients, diarrhea is a common problem that can result from cancer itself or as a side effect of treatment, and can often impede the ability to achieve therapeutic doses of therapy.

Despite the efficacy of tyrosine kinase inhibitors (TKIs) for the treatment of a range of cancers, side effects including treatment-related diarrhea can impede a patient's ability to reach therapeutic doses or stay on therapy.

In this case study, we investigated the outcomes of using crofelemer, a treatment approved for symptomatic relief of noninfectious diarrhea in adult patients living with HIV/AIDS receiving antiretroviral therapy, to treat TKI-induced diarrhea in a 72-year-old male patient with papillary renal cell carcinoma (pRCC).

What was learned from the study?

In this case study, we present a 72-year-old male patient with papillary renal cell carcinoma (pRCC) who experienced TKI-induced diarrhea that was successfully treated crofelemer, a treatment approved for use in patients with HIV-related diarrhea.

This case provides initial evidence that crofelemer can help control diarrhea in pRCC patients receiving cabozantinib.

Going forward, further studies, ideally using a randomized, controlled design, will be required to best ascertain the role of crofelemer in treating targeted therapy-induced diarrhea (TTID) in cancer patients receiving TKIs.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14170604.

CASE PRESENTATION

A 72-year-old man was incidentally found to have renal insufficiency during a primary care visit. Computerized tomography revealed a right renal mass and bulky retroperitoneal and mediastinal lymphadenopathy suggestive of metastatic renal cell carcinoma (RCC). A right radical nephrectomy revealed a 12.1 cm, Fuhrman grade 3 papillary RCC (pRCC) with perirenal and sinus fat invasion.

Two months after surgery, the patient started pazopanib 800 mg daily, a tyrosine kinase inhibitor (TKI) approved for the first-line treatment of metastatic RCC (Fig. 1). This was discontinued after 2 months due to unexpected acute renal failure that required temporary hemodialysis. Second-line treatment with axitinib 5 mg BID was poorly tolerated, with persistent diarrhea, somnolence, cough, difficult-to-control hypertension and worsening renal function. Therefore, axitinib treatment was halted after 1 month. A CT scan 1 month later showed disease progression in the retroperitoneum, mediastinum, and cervical lymph nodes.

He then received the anti-PD-1 antibody nivolumab 240 mg every 2 weeks starting 2 months after axitinib cessation. Though this treatment was well tolerated for 3 months, it had limited efficacy, with disease progression on positron emission tomography/computed tomography (PET/CT), and fine needle aspiration of a new soft tissue mass in the nasopharynx showed progressive pRCC.

Two months after cessation of nivolumab, the patient was started on the TKI cabozantinib at a dose of 60 mg daily. However, in less than 2 months, the treatment had to be halted due to grade 3 diarrhea that was refractory to both loperamide and atropine-diphenoxylate

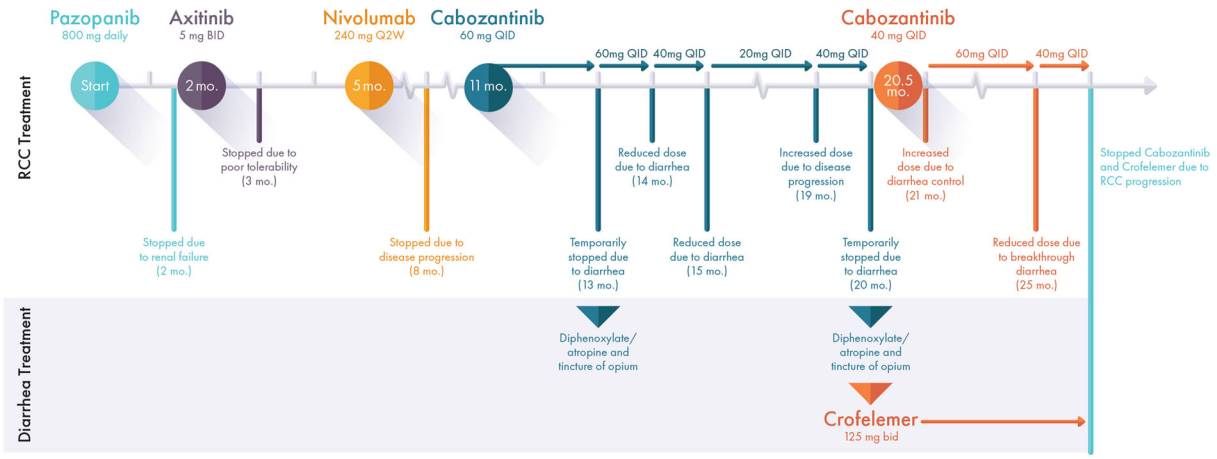


Fig. 1 Timeline showing the patient's course of TKI and diarrhea-related treatment

treatment. Cabozantinib was restarted at full dose 5 days later, but was halted again less than a month later due to diarrhea. Despite the poor tolerance of cabozantinib, restaging PET/CT approximately 5 months after the initiation of therapy showed interval decrease in some of the lymph nodes. Consequently, cabozantinib was restarted at a lower dose of 40 mg daily; however, persistent diarrhea necessitated a further dose reduction to 20 mg daily. PET/CT after a month showed interval decrease in size and hypermetabolism of the metastatic disease (Fig. 2). Four months later, however, new hypermetabolic lymphadenopathy developed, and the cabozantinib dose was raised to 40 mg daily. A month later, the cabozantinib was halted once again due to recurrence of grade 2 diarrhea.

Treatment cessation for 2 days improved diarrhea, but shortly thereafter the patient's condition worsened. Despite being administered diphenoxylate/atropine and tincture of opium (up to 6 mg daily as needed), the patient had episodes of emesis and required hospitalization for dehydration. Workup showed no evidence of clostridium difficile infection, and stool studies including an ova and parasite analysis were negative.

At this point, the providers discussed starting the antidiarrheal crofelemer, given its approval for patients with HIV-related diarrhea. The patient started taking 125 mg BID crofelemer and, within 1 week, his diarrhea ceased and bowel function normalized. Concurrent with crofelemer, the cabozantinib dose was increased to 40 mg daily, which the patient tolerated with normal stools. After 2 weeks on crofelemer, the patient was well-nourished, reported feeling better, and had no acute distress. Given the excellent control of diarrhea with crofelemer, cabozantinib was increased to the original 60 mg daily dose. Although the patient had to occasionally skip cabozantinib doses and supplement with diphenoxylate/atropine or tincture of opium, the diarrhea was overall better controlled. Due to breakthrough diarrhea after 4 months, the cabozantinib dose was decreased to 40 mg daily. One month later, new bony lesions and abdominal carcinomatosis were found on CT, and both cabozantinib and crofelemer were discontinued due to disease progression. Despite subsequent systemic therapy including erlotinib and bevacizumab, the disease worsened, and 3 months later the patient passed away.

After his passing, his next of kin provided consent for publication of this case, and this reporting is in compliance with UCSF Institutional Review Board guidelines for case reporting.

DISCUSSION

Papillary RCC is a relatively uncommon cancer for which the optimal therapy is not known.

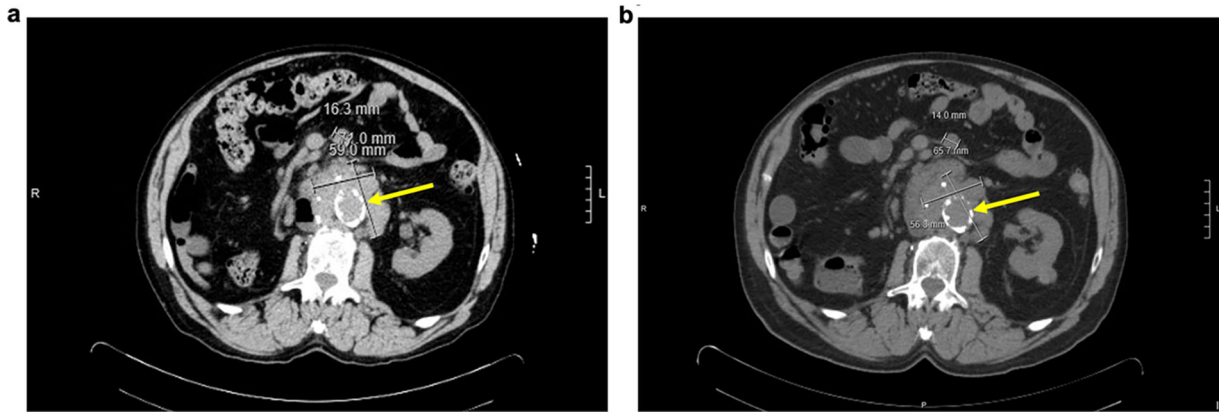


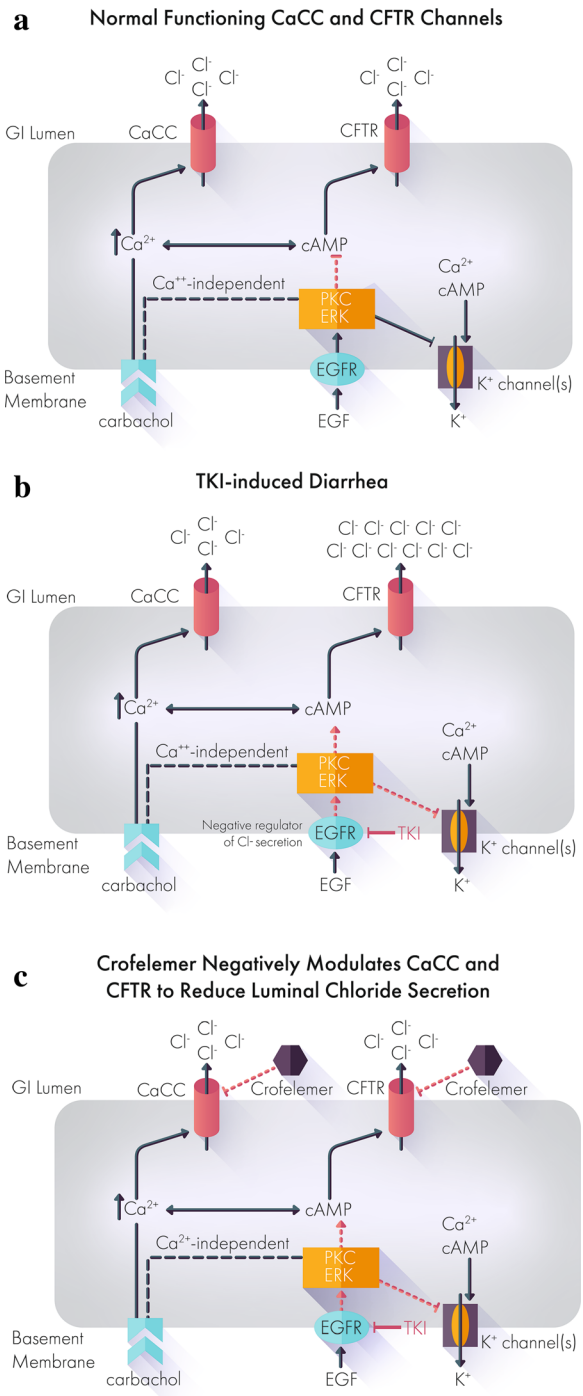
Fig. 2 **a** PET/CT scan conducted on June 2016 showed significant hypermetabolism with a metastatic mass (yellow arrow) measuring 59.0 mm. **b** PET/CT scan conducted on September 2016 displayed reduced hypermetabolism and the metastatic mass measuring 56.8 mm

Given the significant clinical activity of TKIs for clear-cell RCC, a number of studies have shown that some pRCC patients benefit from TKI therapy [1–3]. Consistent treatment with uninterrupted therapeutic doses is essential to optimize patient outcomes. In addition, studies have shown that maximizing TKI doses may confer better anti-tumor activity, although may cause more side effects. For example, in a randomized study of 112 RCC patients, increasing the axitinib dose from 5 to 7 mg BID resulted in both a higher response rate, but more treatment-related toxicity [4].

Diarrhea is a common side effect of many TKIs; however, it is not well understood and is thought to be due to their impact on the bowel epithelium as a result of their vascular endothelial growth factor receptor/epidermal growth factor receptor (VEGFR/EGFR) inhibition, poor intestinal epithelial healing leading to mucosal atrophy [5], alteration of chloride secretion, upregulation of inflammation, and other factors [6, 7] (Fig. 3). Diarrhea occurs in 50–80% of patients [8] and can be subdivided into chemotherapy-induced diarrhea (CID), radiotherapy-induced diarrhea (RID) and targeted therapy-induced diarrhea (TTID) [8, 9]. TTID caused by targeted agents such as epidermal growth factor or tyrosine kinase inhibitors impacts the patient's health overall and their ability to get anticancer treatment [8] and can often impede the ability to achieve effective doses of therapy, either by requiring treatment holidays or dose reductions [10]. In one study of patients with colorectal cancer, treatment-related diarrhea led to dose reduction in 9.5% of the patients [11]. Additionally, a change in regimen and chemotherapy cessation were required in 15.9% and 34.2% of patients, respectively [11].

Pharmacological strategies to manage TTID include the use of loperamide or tincture of opium as a first-line treatment and octreotide as second line [10]. Loperamide and tincture of opium are both opioids that reduce diarrhea by impeding gastrointestinal (GI) motility to delay gastric emptying time [10]. Unfortunately, opioids have high addiction liability [12], and their impact on GI motility can lead to constipation [13]. Second-line octreotide increases intestinal transit time by reducing the secretion of vasoactive intestinal peptide [12]. Octreotide requires TID injections, so both cost and administration logistics are not insignificant [14]. Given the limitations of these current treatment options and the profound impact on cancer treatment, TTID represents a major unmet need.

Crofelemer is a Food and Drug Administration (FDA)-approved drug for symptomatic relief of noninfectious diarrhea in adult patients living with HIV/AIDS receiving antiretroviral therapy [15]. Unlike other medications used for diarrhea, crofelemer exerts its antisecretory



◀**Fig. 3** **a** Chloride ion channels in the intestinal lumen (CFTR and CACC) help to regulate the fluid and electrolyte balance in the GI tract. **b** Tyrosine kinase inhibitors can inhibit EGFR, and activate both basolateral membrane potassium (K+) channels and apical membrane CFTR channels in intestinal epithelia, leading to an imbalance of fluid and electrolytes in the GI tract and causing diarrhea. **c** Crofelemer regulates CFTR and CACC channels to normalize the balance of fluid and electrolytes, resolving symptoms of TKI-induced diarrhea

effects by negatively modulating the CFTR chloride channel and calcium-activated chloride channel at the luminal membrane of enterocytes [16] (Fig. 3). This novel mechanism of action helps restore the fluid and electrolyte balance in the GI tract, leading to symptomatic relief of noninfectious chronic diarrhea in adult HIV/AIDS patients and avoids the development of constipation often observed with opioids. Crofelemer also has negligible oral bioavailability, thus keeping the drug localized to the GI tract and minimizing any significant drug–drug interactions [15].

Our case study presents the off-label use of crofelemer in a 72-year-old patient with metastatic pRCC. We were unable to treat him with cabozantinib at the maximal recommended doses due to treatment-related diarrhea refractory to standard measures including loperamide, tincture of opium and diphenoxylate/atropine. With the administration of crofelemer, bowel function normalized and the cabozantinib dose was able to be increased to the daily recommended dose of 60 mg daily. While ultimately still difficult to control, it is important for clinicians to be aware of this agent when facing difficult choices in treating patients with TKI therapy.

To date, there are over 40 protein kinase inhibitors approved by the FDA for oncological indications [2]. With the increasing frequency of use of kinase inhibitors in cancer treatment, crofelemer may have the potential for wider antidiarrheal applicability in other malignancies being treated with targeted therapies. With fewer interruptions to anticancer treatment regimens due to diarrhea, better clinical

outcomes may be possible. This case provides initial evidence that crofelemer can help control diarrhea in pRCC patients with TTID, including those receiving cabozantinib. Going forward, further studies, ideally using a randomized, controlled design, will be required to best ascertain the role of crofelemer in treating TTID in cancer patients receiving TKIs.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. The authors (CG, BM, STD, and TF) have no personal, financial, commercial or academic conflicts of interest to disclose.

Compliance with Ethics Guidelines. The use of crofelemer was consistent with medical treatment as per FDA guidelines, and was not considered clinical research; therefore, IRB approval was not required. The patient's next of kin provided consent for publication of this case after his passing and prior to manuscript preparation. The data reported here comply with UCSF Institutional Guidelines for decedent case reporting without protected health information.

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