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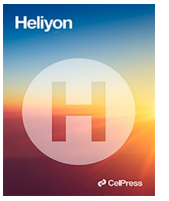

Review article

Mechanism and treatment of diarrhea associated with tyrosine kinase inhibitors

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) have become first-line drugs for cancer treatment. However, their clinical use is seriously hindered since many patients experience diarrhea after receiving TKIs. The mechanisms of TKI-associated diarrhea remain unclear. Most existing therapies are symptomatic treatments based on experience and their effects are unsatisfactory. Therefore, clarification of the mechanisms underlying diarrhea is critical to develop effective anti-diarrhea drugs. This article summarizes several potential mechanisms of TKI-associated diarrhea and reviews current treatment progress.

1. Introduction

Tyrosine kinase inhibitors (TKIs) are targeted drugs that significantly affect cancer, including lung, kidney, breast, and thyroid cancers. They compete with adenosine triphosphate (ATP) for the ATP-binding site of tyrosine kinases or induce structural changes in tyrosine kinases, thereby reducing tyrosine kinase phosphorylation and interfering with the growth, proliferation, and metastasis of cancer cells [1,2]. The high efficacy of TKIs is accompanied by adverse events (typically diarrhea) during clinical treatment. The incidence of all-grade diarrhea in the absence of anti-diarrhea prophylaxis varies from 7.1 to 98.4% depending on the agent [3–6]. Diarrhea may cause dehydration, electrolyte imbalance, and renal insufficiency which reduces patients' health-related quality of life and compliance. Furthermore, dose reductions and treatment discontinuation due to diarrhea may compromise clinical outcomes [7]. Therefore, prophylaxis and management of diarrhea are important for improving the prognosis. There are many targets of TKIs [2]; however, the highest rate of diarrhea is associated with those targeting epidermal growth factor receptor (EGFR, also named ErbB1) and vascular endothelial growth factor receptor (VEGFR). This article summarizes several potential mechanisms of diarrhea induced by EGFR-TKIs and VEGFR-TKIs and reviews targeted therapeutic drugs and comprehensive management measures.

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2. Clinical characteristics of TKI-associated diarrhea

Diarrhea is a common side effect of several cancer treatments including chemotherapy, radiotherapy, and targeted therapy. This is the most common adverse event associated with TKI treatment. The toxicity of TKIs increases with a greater number of targets. Second-generation EGFR-TKIs (irreversible pan-EGFR inhibitors) can block multiple EGFR family members and result in a higher incidence of diarrhea compared with first- and third-generation TKIs [5]. A meta-analysis of 16 trials and 2535 patients with non-small cell lung cancer showed that the diarrhea risk following afatinib treatment (second-generation EGFR-TKI, 91.7%) was twice as high as that following erlotinib (first-generation EGFR-TKI, 42.4%) or gefitinib (first-generation EGFR-TKI, 44.4%) ($p < 0.01$) [8]. TKI-associated diarrhea typically occurs early during the treatment, mostly in the first month. The severity is related to the type and dose of drugs, mainly 1–3 grade diarrhea [3–6,9]. Currently, loperamide is used to relieve diarrhea symptoms caused by TKIs. However, it does not target this mechanism, and the effect is not always satisfactory [5].

3. Potential mechanisms of TKI-associated diarrhea

3.1. EGFR-TKI-associated diarrhea

3.1.1. Intestinal mucosal damage

In addition to being expressed in cancer cells, EGFRs are abundantly found in healthy intestinal epithelial cells. They cause a cascade of complex signaling pathways to regulate the proliferation, differentiation, migration, and apoptosis of intestinal epithelial cells [10]. Direct inhibition of EGFR by TKIs may reduce the growth and healing of the intestinal epithelium, cause mucosal damage, and lead to diarrhea. This hypothesis was supported by an *in vitro* experiment showing that lapatinib inhibits growth and induces late apoptosis in normal intestinal epithelial cells (IEC-6), and has stronger toxicity in IEC-6 cells than in breast tumor cells [11]. Moreover, lapatinib is associated with diarrhea in rats; this is caused by a reduction in EGFR expression in jejunal crypts and dose-dependent changes in crypt length, mitotic rate, and goblet cell morphology [12]. Endoplasmic reticulum (ER) stress may contribute to EGFR-TKI-induced apoptosis in IEC-6 cells. Gefitinib and icotinib dramatically trigger the RNA-dependent protein kinase-like ER kinase pathway and the transcriptional induction of XBP-1 signaling in ER stress [13]. A recent study investigated the molecular mechanisms of gefitinib-induced toxicity in three-dimensional innovative cell models of the human colon and small intestine [14]. Cytotoxicity and transcriptomic data corroborated that gefitinib downregulates EGFR-regulated genes (*AURKA*, *CCND1*, *c-MYC*, *c-FOS*, and *FGF19*), upregulates p53 and FOXO-regulated genes, hampers cell cycle progression and cell differentiation, and promotes cell apoptosis [14]. In addition, EGFR-TKIs can destroy mucosal integrity by disrupting tight junctions, resulting in intestinal epithelial barrier dysfunction [13–16].

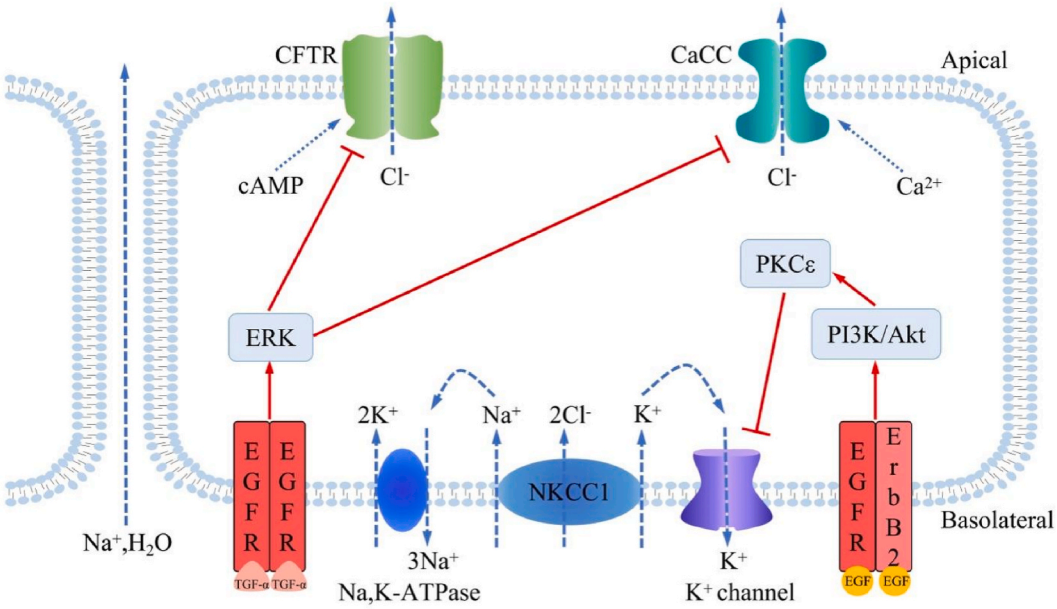

Fig. 1. Chloride secretory mechanism in normal intestinal epithelium (blue dotted line) and negative regulation of chloride secretion by EGFR (red solid line). NKCC1: sodium-potassium chloride co-transporter type 1; CFTR: cystic fibrosis transmembrane conductance regulator; CaCC: calcium-activated chloride channels; cAMP: cyclic adenosine monophosphate; EGFR: epidermal growth factor receptor; ErbB2: human epidermal growth factor receptor 2; EGF: epidermal growth factor; TGF-α: transforming growth factor-α; ERK: extracellular regulated protein kinase; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; PKC: protein kinase C. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.1.2. Inflammation

A rat model of neratinib-induced diarrhea suggests that inflammation may also contribute to the pathogenesis of diarrhea. In this model, neratinib causes inflammation and anatomical disruption in the ileum and colon [17]. Subsequently, budesonide (a corticosteroid with anti-inflammatory activity) reduces neratinib-induced diarrhea by increasing the anti-inflammatory IL-4 tissue concentration and reducing histopathological injury in the colon [17]. Gefitinib significantly promotes the expression of IL-6 and IL-25 in IEC-6 cells; this suggests that it plays a role in intestinal inflammation [13]. Increased levels of pro-inflammatory factors such as monocyte chemoattractant protein-1 were found in rat intestinal tract following treatment with dacomitinib [15,16]. There is no evidence that EGFR-TKIs directly initiate inflammatory pathways. Intestinal mucosal damage usually occurs along with inflammation; therefore, there may be an interaction between the two.

3.1.3. Increased chloride secretion

Increasing evidence suggests that chloride secretion may participate in the development of EGFR-TKI-associated diarrhea. Chloride is the predominant electrolyte driving intestinal fluid secretion. Chloride secretion is accompanied by the paracellular movement of sodium, and the resulting luminal accumulation of sodium chloride provides an osmotic basis for water movement [18]. Several transmembrane transporters are involved in chloride secretion by intestinal epithelial cells (Fig. 1). Chloride enters the cell across the basolateral membrane via the sodium-potassium chloride co-transporter (NKCC1) and exits into the intestinal lumen through the cAMP-dependent cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels and calcium-activated chloride channels (CaCC) located in the apical membrane [18]. The electrical driving force for chloride secretion is created by a sodium-potassium ATPase pump in concert with potassium channels [18,19].

EGFRs are abundantly expressed in the basolateral membranes of intestinal epithelial cells. Chloride secretory responses are intrinsically restrained by many EGFR signaling mechanisms (Fig. 1). Binding of ligands to EGFR in intestinal epithelial cells leads to homodimerization and heterodimerization with ErbB2; this recruits distinct downstream signaling pathways and finally decreases chloride secretion [20]. The downstream pathways include the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB, also known as Akt) and protein kinase C (PKC) pathways that inhibit potassium channels, and extracellular regulated protein kinase (ERK) pathways that inhibit chloride channels [20,21]. EGFR-TKIs inhibit the negative regulation of chloride secretion by EGFR; this results in excessive chloride movement into the lumen, which causes secretory diarrhea [22].

The effect of EGFR-TKIs on chloride secretion is supported by research using afatinib. Afatinib amplifies chloride secretion stimulated by carbachol (a calcium agonist), and this amplifying effect can be blocked by CFTR and potassium channel inhibitors [23]. Similarly, erlotinib potentiates calcium-dependent chloride secretion. Both afatinib and erlotinib reduce the phosphorylation of EGFRs and downstream Akt and ERK1/2 in T84 human colonic carcinoma cells [24]. In addition, CaCC inhibitors attenuate diarrhea in rats treated with osimertinib and afatinib; this suggests that EGFR-TKI-associated diarrhea may be partially mediated by CaCC activation [25]. In contrast, crofelemer (a dual inhibitor of CFTR and CaCC) does not alleviate or even aggravate dacomitinib-induced diarrhea; however, there is severe tissue damage and disruption of the tight junction in the rat ileal epithelium [15]. Lapatinib has no significant effect on serum chloride levels in rats [26]. This may indicate that the mechanism of diarrhea induced by different drugs is different, or that increased chloride secretion is a short-term acute response to the drug, while mucosal injury is a long-term result.

3.2. VEGFR-TKI-associated diarrhea

3.2.1. Intestinal mucosal ischemia

VEGFR-TKIs can inhibit the vascular system of tumors and affect the blood supply to normal organs. VEGF and VEGFR are widely expressed in the intestinal epithelium [27], and addition of VEGF(R) inhibitors significantly reduces the capillary network in pancreatic islets and intestinal villi [28]. Small perturbations in the intestinal mucosa blood flow can lead to rapid metabolic changes characteristic of ischemia and resultant hypoxia which are related to diarrhea [29]. A retrospective case analysis reports that intestinal mucosal changes in patients treated with bevacizumab (VEGF monoclonal antibody) are consistent with ischemic colitis [30]. Therefore, VEGFR-TKIs may cause intestinal mucosal ischemia and induce diarrhea. This assumption is supported by a recent study wherein the intestinal vessels regressed within a few days after VEGFR gene deletion [31]. VEGFR2 inhibition by sorafenib leads to epithelial hypoxia and diarrhea, and the rs4864950 variant in the kinase insert domain receptor gene encoding VEGFR2 increases the risk of diarrhea [32].

3.2.2. Pancreatic exocrine dysfunction

Pancreatic exocrine dysfunction leads to malabsorption and other disorders such as celiac disease, lactose intolerance, and short bowel syndrome [33]. Steatorrhea developed in seven patients treated with sorafenib, and five patients showed dramatic improvement (grade 2 to grade 0) within 1 week after receiving pancreatic enzyme supplements [34]. This suggests that pancreatic exocrine dysfunction may be involved in the occurrence of diarrhea. Indeed, VEGFR inhibitors increase serum amylase and lipase levels and reduce zymogen granules in the pancreas [35]. VEGFR-TKIs can also lead to reduced pancreatic volume. Pancreatic atrophy is reported in patients after long-term sorafenib treatment [36]. A CT scan shows that the pancreatic volume significantly decreases following treatment with sorafenib and bevacizumab; this is most likely due to a reduced microvasculature by the inhibition of VEGF [28,37].

3.3. Fibroblast growth factor receptor (FGFR)-TKI-associated diarrhea

FGFR-TKI-associated diarrhea may be the result of excess bile acid synthesis. Bile acid synthesis in hepatocytes is inhibited by

fibroblast growth factor-19 (FGF-19)-mediated feedback. FGF-19 binds to FGFR4 on the hepatocyte cell membrane, triggering intracellular signaling in a klothoβ-dependent manner to downregulate cholesterol 7a-hydroxylase expression and thereby suppress bile acid synthesis [38]. FGFR-TKIs may disrupt this feedback inhibition by blocking FGFR4, leading to excess bile acid synthesis. Excessive bile acids entering the colon can cause accelerated colonic transit and increased colonic mucosal permeability, resulting in bile acid diarrhea [39]. Increased total fecal bile acids and FGFR4 gene variants also have been observed in some patients with irritable bowel syndrome-diarrhea [40]. The first-in-human study of INCB062079 (a selective FGFR4 inhibitor) shows diarrhea is the most common toxicity [41], indicating the inhibition of FGFR4 may cause diarrhea. However, there are no studies on bile acid synthesis in patients with diarrhea after FGFR-TKI treatment. This potential mechanism needs further study.

3.4. Multitarget TKI-associated diarrhea

3.4.1. C-KIT inhibited by multitarget TKIs

Many TKIs are multitarget inhibitors. Imatinib blocks the activity of BCR-ABL, c-KIT, and the platelet-derived growth factor receptor (PDGFR) [42]. The frequency of diarrhea under imatinib seemed higher than asciminib, which only inhibits BCR-ABL1 [43]. Besides, cediranib and axitinib (both VEGFR-TKIs) also inhibit c-KIT and PDGFR. Treatment with cediranib and axitinib has a higher incidence of diarrhea than bevacizumab [44]. This may involve the inhibition of c-KIT. C-KIT is a receptor tyrosine kinase that is expressed by interstitial cells of Cajal (ICCs) and regulates the normal development and survival of ICCs [45,46]. ICCs are pacemaker cells of the intestine that can generate and propagate slow waves. Moreover, they are adjacent to the nerve fibers of the myenteric plexus and transduce inputs from enteric motor neurons to regulate intestinal rhythmic contractions [47]. Imatinib and sunitinib [48,49] may affect the function of ICCs by inhibiting c-KIT, leading to intestinal motility disorders and diarrhea.

3.4.2. Gastrointestinal tract submucosal fat deposition

Gastrointestinal tract submucosal fat (SMF) deposition is observed in patients receiving multitarget TKIs [50]. A retrospective analysis of abdominal CT scans of 63 patients shows that all patients with positive SMF receive multitarget TKIs (pazopanib or sunitinib) while none of the patients treated with single-target TKIs (osimertinib, afatinib, erlotinib, or gefitinib) develop SMF (17.5% vs. 0%; $p = 0.04$). Diarrhea is more common in patients who develop SMF [50]. Gastrointestinal tract SMF deposition in patients treated with multitarget TKIs might represent intestinal lymphangiectasia, a disease resulting in protein-losing enteropathy with malabsorption symptoms, including diarrhea [50,51]. However, there is no study determining SMF in patients receiving TKIs.

3.5. Common mechanisms that may occur in all TKIs

3.5.1. Changes in the gut microbiome

The gut microbiome mediates inflammatory responses via the innate immune system and plays a key role in chloride secretion

Table 1
The clinical studies and basic experiments on mechanisms of TKI-associated diarrhea.

Targets associated with diarrhea	Mechanisms	TKIs	Subjects	References
EGFR	Intestinal mucosal damage	Lapatinib	IEC-6 cells	[11]
			Rats	[12]
		Gefitinib	IEC-6 cells	[13]
			Human healthy colon and small intestine organoids	[14]
		Dacomitinib	T84 cells, Rats	[15,16]
	Inflammation	Neratinib	Rats	[17]
		Gefitinib	IEC-6 cells	[13]
		Dacomitinib	T84 cells, Rats	[15,16]
	Increased chloride secretion	Afatinib	T84 cells, Rats	[23]
		Afatinib, Erlotinib	T84 cells, Enteroid-derived monolayers from human	[24]
		Afatinib, Osimertinib	Rats	[25]
VEGFR	Intestinal mucosal ischemia	Sorafenib	Human	[32]
	Pancreatic exocrine dysfunction	Sorafenib	Human	[34,36,37]
Multitargets[a]	Gastrointestinal tract submucosal fat deposition	Pazopanib, Sunitinib	Human	[50]
Gut microbiome	Changes in the gut microbiome	Sunitinib, Sorafenib, Pazopanib, Axitinib	Human	[54,55]
		Neratinib	Human	[56]
CYP3A4, ABCB1/G2	Drug metabolism	Afatinib	Human	[60,61]
		Neratinib	Rats	[62]

[a] The specific target of pazopanib and sunitinib inducing gastrointestinal tract submucosal fat deposition is unknown. TKIs: tyrosine kinase inhibitors; EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; IEC-6: intestinal epithelial cell-6; CYP3A4: cytochrome P450 (CYP) 3A4; ABCB1/G2: ATP-binding cassette (ABC) transporter B1 and G2.

[52]. Its diversity and composition can influence drug metabolism, the host immune system, and the intestinal barrier [53]. Thus, the gut microbiome may change after exposure to TKIs, causing diarrhea. The first study profiling stool bacteria to ascertain the etiology of VEGFR-TKI-related diarrhea in patients with metastatic renal cell carcinoma shows that *Bifidobacterium* species are scarcer in patients with diarrhea than in those without diarrhea [54]. Additionally, patients receiving VEGFR-TKIs have a lower relative abundance of *Bifidobacterium* species than healthy subjects, with diarrhea patients having higher levels of *Bacteroides* species and lower levels of *Prevotella* species [55]. Gut microbiome changes also occur after EGFR-TKI treatment. For instance, neratinib increases *Ruminococcaceae* and *Oscillospira* and decreases *Blautia* in rat intestines [56]. Further clarification is required to determine whether microbiome changes cause diarrhea or whether diarrhea causes microbiome changes. The gut microbiome is susceptible to multiple factors; therefore, further work is required to determine whether TKIs are responsible for these changes.

3.5.2. Drug metabolism

Generally, genetic polymorphisms of drug-metabolizing enzymes and transporters directly or indirectly influence the efficacy and toxicity of various drugs, thereby causing interindividual differences in drug response [57,58]. Tyrosine kinase inhibitors are primarily metabolized by cytochrome P450 (CYP) 3A4 and transported by efflux ATP-binding cassette (ABC) transporter B1 and G2 [59]. Afatinib plasma concentration correlates with the severity of diarrhea in the early phase of treatment [60,61]. Patients carrying the A allele of *ABCG2* C421A have higher afatinib plasma concentrations and more severe diarrhea [60]. An afatinib plasma trough concentration (C0) greater than or equal to 28.5 ng/mL might be used as a cut-off value to ascertain the incidence of afatinib-induced grade 2 diarrhea; the authors recommend monitoring the C0 of afatinib on day 8 after afatinib therapy initiation [61]. Tyrosine kinase inhibitors may inhibit some of their own metabolizing enzymes and transporters [59]: neratinib downregulates intestinal CYP3A enzyme to cause excessive drug disposition and eventually leads to gut injury [62]. In conclusion, drug-metabolizing enzymes and transporters determine the level of drug exposure and influence toxicity.

The clinical studies and basic experiments on mechanisms of TKI-associated diarrhea are summarized in Table 1.

4. Current treatment progress of TKI-associated diarrhea

Glucagon-like peptide of type 2 (GLP-2) is a naturally occurring gut hormone that can reduce intestinal motility and permeability. Additionally, it also stimulates crypt cell proliferation and has an anti-apoptotic mechanism. Elsiglutide is a selective long acting GLP-2 and has been shown to decrease incidence and severity of lapatinib-induced diarrhea in rats. This may be due to thickening mucosa, leading to increased surface area for fluid absorption in the distal small intestine [63].

Crofelemer is a purified proanthocyanidin oligomer extracted from the bark latex of *Croton lechleri*. It has a dual inhibitory action on CFTR and CaCC and significantly improves secretory diarrhea [64]. Its bioavailability is very low (with little to no systemic absorption) after oral administration; therefore, its toxicity is minimal beyond mild gastrointestinal effects [65]. Crofelemer received US FDA approval in December 2012 for the symptomatic relief of non-infectious diarrhea in adult patients with human immunodeficiency virus (HIV) receiving anti-retroviral therapy [66]. Crofelemer successfully controlled cabozantinib-related diarrhea in a 72-year-old patient [67]. The latest results of a phase II randomized study (HALT-D) report that crofelemer reduces the incidence and severity of diarrhea in patients with breast cancer receiving trastuzumab, pertuzumab, and taxane [68]. The phase III OnTARGET trial (NCT04538625) evaluating the prophylaxis efficacy of crofelemers for targeted therapy-induced diarrhea is ongoing.

Budesonide and bile acid sequestrants may relieve diarrhea caused by TKIs. Bile acid sequestrants such as colesevelam and colestipol are used to treat bile acid malabsorption and subsequent diarrhea [69]. Budesonide and colesevelam alleviate neratinib-associated diarrhea in rats [17]. The phase II control trial of different anti-diarrheal strategies for neratinib-associated diarrhea reveals that loperamide combined with budesonide or colestipol further reduces the incidence of grade 3 diarrhea compared with loperamide alone (31% for loperamide alone, 28% for budesonide + loperamide, and 21% for colestipol + loperamide) [70].

Fructus mume has antibacterial and anti-inflammatory properties and is used to treat chronic diarrhea via its anti-inflammatory activities in Asian countries [71,72]. Extracts of *F. mume* (EFM) reduce diarrhea and gastrointestinal symptoms caused by lapatinib and capecitabine; this may be a potential choice for TKI-induced diarrhea therapy. There are three active components in EFM: citric acid, 5-hydroxymethylfurfural, and chlorogenic acid [73].

Two recent studies reported that ramosetron improves nintedanib-induced diarrhea [74]. Ramosetron is a serotonin (5-hydroxytryptamine, 5-HT) type 3 receptor inhibitor that treats diarrhea-predominant irritable bowel syndrome by slowing intestinal transit [74]. There may be an association between TKI-induced diarrhea and 5-HT. Diarrhea induced by imatinib is associated with polymorphisms in the 5-HT reuptake transporter gene [75].

Distinct microbial profiles are observed in patients with TKI-associated diarrhea. In principle, probiotics, and fecal microbiota transplantation modulate the gut microbiota and are possible treatment options for this condition. Fecal microbiota transplantation is more effective and safe than probiotics [76]. This may be owing to its ability to deliver a diverse microbiome with a greater bacterial load [53]. Diarrhea was resolved 4 weeks after fecal microbiota transplantation in seven of ten patients receiving fecal microbiota from healthy donors compared to none of ten patients in the placebo group (70% vs. 0%) [77]. Successful engraftment is observed in subjects receiving donor feces mainly involving *Akkermania muciniphila*, *Alistipes putredinis*, and *Barnesiella intelinhominis*; these strains may play a role in diarrhea relief [77].

5. Comprehensive management strategies of TKI-associated diarrhea

Currently, most therapies for TKI-associated diarrhea are symptomatic treatments based on experience. Patient education is critical to reduce the incidence of diarrhea and provide prompt treatment. Doctors need to inform patients of the potential side effects of TKI treatment before initiation, especially those with risk factors for severe diarrhea including the female sex, low body weight (<45 kg), and older age (≥60 years) [78]. Written recommendations should be provided to patients at the onset of therapy, including providing information about the anti-diarrhea diet with a list of prophylactic and therapeutic foods, advice on daily fluid intake, and a checklist of alarm signals [79]. Loperamide prophylaxis and dose escalation reduce the incidence, severity, and duration of neratinib-associated diarrhea [70,80–82]. Loperamide is an opioid receptor agonist in the gastrointestinal tract which may decrease gut motility. High-dose loperamide is the first-line treatment for many types of diarrhea [5].

The occurrence of diarrhea in patients receiving TKIs should be initially analyzed to determine whether it is caused by TKIs. It is necessary to distinguish between infective diarrhea, neutropenic septic diarrhea, chemotherapy-induced diarrhea, and TKI-associated diarrhea in patients treated with TKIs and chemotherapy. Diarrhea is then managed based on its severity and related complications [83]. Diarrhea is currently classified according to the Common Terminology Criteria for Adverse Events (CTCAE v5). Complications of diarrhea include infection, dehydration, lightheadedness when standing, bleeding, oliguria or anuria, fever (>37.5 °C for over 4 h or >38 °C), weight loss ≥2 kg, worsening colicky abdominal pain, and marked malaise [84,85]. Patients with grade 1 or 2 diarrhea without complications should adjust their diet by eating small, frequent meals (such as bananas, rice, apples, and toast), increasing fluid intake, and removing all lactose-containing products and alcohol from their diet. The administration of anti-diarrhea agents such as loperamide, atropine, or racecadotril can solve most grade 1 or 2 diarrhea. Patients with grade 1 or 2 diarrhea accompanied by complications or grade ≥3 diarrhea usually require dose reduction or treatment interruption with TKIs (and even hospital admission when necessary) in addition to the above measures. The doctor can decide whether to restart the treatment and adjust the dose and treatment cycle according to individual conditions after the diarrhea stops [84–86].

6. Conclusions

Tyrosine kinase inhibitor-associated diarrhea is a barrier to the optimal treatment of patients with cancer. The toxicological mechanism of diarrhea is poorly understood. The current hypothesis mainly involves mucosal damage, ion secretion, inflammation, ischemia and hypoxia, pancreatic exocrine, and intestinal movement, depending on different drug targets. Other possibilities include non-target factors such as the gut microbiome and drug metabolism. It is more than likely that several mechanisms participate in TKI-associated diarrhea, and interplay occurs among each mechanism. Therefore, larger and more comprehensive studies are required to clarify the key mechanisms underlying diarrhea. The differences between the research results may indicate that the mechanism of diarrhea caused by different drugs is distinct. Therefore, it is necessary to separately study each drug. A large number of samples should be statistically analyzed to determine the risk factors for diarrhea to manage diarrhea more effectively. Patients with high-risk factors should be accurately targeted for active prophylaxis and treatment. In conclusion, effective control of diarrhea and optimal treatment results are only achievable after clarifying the mechanism of TKI-associated diarrhea and developing targeted therapy.

Data availability statement

No data was used for the research described in the article.

Ethics statement

Review and/or approval by an ethics committee was not needed for this study because this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. Informed consent was not required for this study because this article does not involve any patient information.

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CRediT authorship contribution statement

Jiangnan Liu: Writing – original draft, Methodology, Investigation, Conceptualization. **Shuai Yan:** Investigation. **Juntong Du:** Investigation. **Lizhi Teng:** Investigation. **Ru Yang:** Investigation. **Peng Xu:** Investigation. **Weiyang Tao:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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