Journal of Clinical & Experimental Pathology

Kee BK et al., J Clin Exp Pathol 2018, 8:3
DOI: 10.4172/2161-0681.1000350

Review Article Open Access

Role of Bacterial Translocation in the Progressive and Delayed Irinotecan-Induced Diarrhea

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Received date: August 30, 2018; **Accepted date:** September 19, 2018; **Published date:** September 29, 2018

Abstract

Irinotecan is a pro-drug of SN-38 primarily used for the treatment of colorectal cancer and used for other type of cancers either alone or combined with other chemotherapeutic drugs. A major dose limiting side effect of irinotecan is the late-onset diarrhea. The mechanism of irinotecan-induced diarrhea is not entirely understood and current approaches to prevent diarrhea are not quite effective in many patients. Recent evidences showed that gut microflora plays an important role in irinotecan-induced diarrhea. In this paper, we summarized the gut toxicity of irinotecan, the possible mechanism, the role of bacterial translocation, and clinical perspectives. The goal is to facilitate a better understanding of the role of bacterial translocation in regulation of irinotecan disposition and toxicity, and the potential implications in patients.

Keywords: Irinotecan; Diarrhea; Bacteria translocation

Introduction

Irinotecan (CPT-11, Camptosar®) is a semi-synthesized water-soluble prodrug of 7-Ethyl-10-hydroxy-camptothecin (SN-38) derived from camptothecin, a natural compound isolated from the bark and stem of Camptotheca acuminate [1]. Irinotecan is approved by the FDA as the first-line drug to treat metastatic colon cancer (mCRC) and is currently under active investigations to treat different types of malignant such as lung, pancreatic, ovarian, cervical, prostate, and gastrointestinal cancers [2-6]. The mechanism of action is that the drug (i.e., its active form SN-38) can inhibit topoisomerase I to interrupt DNA synthesis in cancer cells [7,8]. Irinotecan can be used alone or in combination with other drugs such as in combination with 5-FU/leucovorin [9,10].

Despite the promising efficacy, irinotecan clinical usage is limited due to side effects including vomiting, nausea, diarrhea, constipation, neutropenia, weakness, fever, pain, abnormal liver function, hair loss, etc. Among these side effects, diarrhea is one of the major dose-limiting side effects that may affect clinical outcomes. A few of papers have reviewed the incidences, possible mechanism, and preventive/therapeutic approaches [11-13]. The aim of this paper is to review the role of bacterial translocation (BT) in the progressive and delayed irinotecan gut toxicity.

Irinotecan gut toxicity

Diarrhea is one of the major dose-limiting toxicities of irinotecan: Irinotecan can cause early-onset and late-onset diarrhea. The early-onset, which is characterized by rapid-onset diarrhea and may also include abdominal cramping and diaphoresis, occurs within 24 hours of drug administration, while the late-onset occurs after 24 hours of drug administration. The early-onset diarrhea can be effectively controlled by atropine [14,15]. However, the late-onset diarrhea, which is inconsistent, unpredictable, non-cumulative, dose dependent, with wide interpatient and intra-patient variability, is a much more serious problem that may affect patients' quality of life and may cause early death either directly from life-threatening sequelae or indirectly from adjustments in chemotherapy plan [16,17].

Incidence of diarrhea induced by irinotecan is significant: The overall incidence of diarrhea ranges from 60% to 87%, including up to 40% of severe late-onset diarrhea (grade 3 and 4), which appears to be dose-dependent [18,19]. The median time to onset ranged from 5 to 11 days after drug administration and the diarrhea duration last for 2 to 5 days depend on the dosing schedule [16,20]. The incidence of diarrhea using the common regimens is listed in Table 1.

Most of the patients need diarrhea treatment using anti-diarrhea agents (e.g., loperamide, octreotide). Although standard diarrhea management is recommended, around 10% of patients who developed diarrhea require hospitalization or even change the chemotherapy plan (e.g., dose reduction), which significantly affect the clinical outcomes and even cause early death [16,21].

Neutropenia is another dose-limiting toxicity of irinotecan: Neutropenia, which can be ameliorated or prevented using growth factors such as G-CSF, is a short duration and reversible dose limiting side effect of irinotecan. Compared to diarrhea, neutropenia is less frequent and easily managed.

Dosage	and	Dose Regimens	Diarrhea Incidence	References
Administration			**(total/grade 3-4)**	
Irinotecan		Weekly, 125 mg/m^2 intravenous infusion over 90	>82 % / >36%	[93]
		minutes on days 1, 8, 15, 22 then 2-week rest		
Irinotecan		Every 3 weeks 350 or 300 mg/m^2 intravenous infusion	>76 % / >19%	[93]
		over 90 minutes on day 1 every 3 weeks		
Irinotecan/LV/5-FU		Irinotecan 180 mg/m^2 intravenous infusion over 90	<51%/<17%	[94-98]
		minutes on days 1, 15, 29 with LV 200 mg/m^2 intravenous infusion over 2 hours on days 1, 2, 15, 16,29, 30 followed by 5-FU 400 mg/m^2 intravenous bolusinfusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30.		

Table 1: Diarrhea incidence using the FDA approved irinotecan dosage and administration for the treatment of colorectal cancer.

For example, a clinical study showed that grade 3-4 diarrhea affected 22% of the metastatic colorectal cancer patients receiving irinotecan plus 5-FU/leucovorin treatment, while only 5% of the patients developed grade 3-4 neutropenia [22]. Another clinical study showed that even at a dosage of 750 mg/m^2 of irinotecan, the maximum tolerated dose for the risk of severe neutropenia was not reached [23].

Dose reduction is an approach in managing irinotecan-induced diarrhea: Dose reduction and/or changing in dosing regimens are frequently used to manage irinotecan-induced diarrhea. For example, it is reported that the grade 3-4 diarrhea incidence reduced from 57.1 % to 10.8 % in colonic cancer patients carrying TA7/TA7 allele (UGT1A1 promoter) when irinotecan's dose was reduced from 350 mg/m^2 3-weeky to 250 mg/m^2 3-weeky [24]. However, it is highly suspected that dose reduction will affect the therapeutic effect as tumor suppression is correlated with *in vivo* exposure of SN-38. In fact, recent clinical reports clearly indicate that many patients could benefit from higher doses [23,25-30].

Mechanisms of gut toxicity

Diarrhea is caused by GI damage: The mechanisms underlying diarrhea induced by irinotecan is not entirely understood. The complex etiology of irinotecan-induce diarrhea seems to involve changes in the absorption of fluids and electrolytes, intestinal motor dysfunction, and inflammation of the mucosal membranes lining the gastrointestinal tract [12,31]. Molecular mechanism studies revealed that early-onset diarrhea induced by irinotecan is associated with parasympathetic discharge, stimulation of serotonin receptors, and release of thromboxane A2 (TX-A2),[12,20] while the molecular mechanism of late-onset diarrhea is not fully understood but is correlated with direct damage to the intestinal mucosa by SN-38. Understanding the disposition of irinotecan provides insight into the mechanism of late-onset diarrhea.

Irinotecan disposition is associated with colonic exposure of SN-38: Irinotecan's disposition has been well studied [32]. The drug is administrated through i.v. route and is activated to SN-38 by carboxylesterases (CEs) in the plasma or liver. The active drug (i.e., SN-38) is then transferred and distributed to different organs including the tumor tissue. The free SN-38 can be conjugated into SN-38 glucuronide (SN-38G, a non-effect, non-toxic metabolite) mediated by uridine 5'-diphospho-glucuronosyl-transferase (UGT) 1A subfamily. SN-38 was shown to induce intestinal inflammation and oxidative stress, leading to gut damage [12,33,34]. The colonic SN-38 comes from different sources. SN-38 in the liver can be excreted via different hepatic efflux transporters (e.g., i.e., P-gp, MRP2, BCRP) through bile into small intestine and then enters the colon (Figure 1).

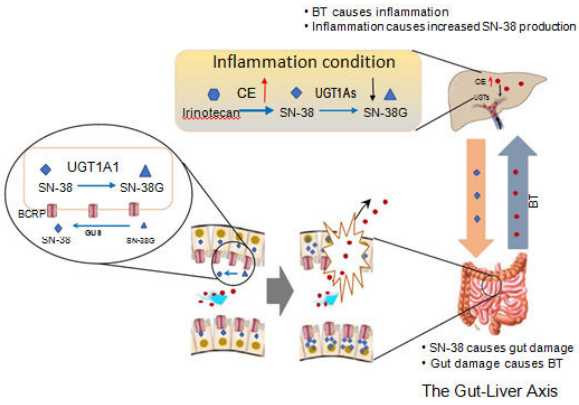

Figure 1. Schematic gut -liver axis. In the intestine, SN-38, which is controlled by *UGT1A1*, BCRP, and bacterial GUS, is accumulated in the epithelium and the gut was eventually damaged, resulting in bacteria translocation from the gut to the liver. In the liver, bacteria translocated from the gut causes inflammation, leading to improved SN-38 production due to downregulated *UGT1A1* and upregulated CE expressions. The improved SN-38 production in the liver will lead to enhanced biliary secretion.

Moreover, irinotecan and SN-38G can also be secreted from the liver into the small intestine, where these two non-toxic compounds can be converted into free SN-38 by intestinal CEs or by microflora, respectively. Mass balance study using 14-carbon labelled irinotecan have demonstrated that the fecal route of excretion, mainly from biliary excretion, is the major route eliminating more than 60% of the

administered drug,[35] although there are other competing metabolic/excretion pathways of irinotecan facilitated by cytochrome P450 (CYP) enzymes [36].

Other than biliary secretion, the enterocytes also secrete these three compounds, [37,38] however, the amounts of these compounds secreted from intestine are significantly lower than those from bile [38]. In addition, free SN-38 can be re-absorbed in the intestine and reach the liver through the portal vein to form an enterohepatic recycling (EHR) (Figure 1), resulting in prolonged half-life and repeated exposure in the gut. For example, it is reported that SN-38 presented in human plasma for 3 weeks after a single irinotecan i.v. infusion at a dose of 350 mg/m^2 [39]. More importantly, when the gut is damaged by SN-38, viable bacteria or endotoxins will translocate from the gut to the liver, where CE and *UGT1A1* expression will be affected, resulting in enhanced SN-38 biliary secretion and more gut damage (see detail later). This endocrine cycle aggravates diarrhea condition.

SN-38-induced intestinal microbiota changes: Studies using animal models have indicated that changes in the microflora of the gut as possible cause, at least in part, for late-onset diarrhea [40]. It has been shown that chemotherapy treatment is associated with a deregulated intestinal microbial homeostasis and a decreased microbial diversity [41]. Likewise, unbalanced bacterial population (dysbiosis) was observed with irinotecan treatment. In rats a relative increase or decrease in the presence of certain bacteria in stomach, jejunum, colon and feces were observed in the irinotecan-treated group compared to the control group. In colon of irinotecan-treated rats, an increasing trendin *Escherichia spp., Clostridium spp., Enterococcus spp., Serratia spp. and Staphylococcus spp.* was noticed, whereas, in fecal samples, increase in *Proteus spp., Clostridium spp.,* and *Peptostreptococcus spp.* was associated with a decrease in *Bacillus spp.,* and *Bifidobacterium spp.* [42]. Irinotecan treatment reduced the colony of good bacteria, Clostridium cluster IV (cluster which contains Butyrate-producing *Clostridium spp.*) and in contrast increased β-glucuronidases (GUS) producing bacteria (such as *Enterobacteriaceae spp.*), [43] that deconjugates irinotecan metabolite, SN-38 glucuronide (SN-38G) back to the toxic metabolite SN-38 in the intestine. Also, a decrease in total bacterial count has also been reported with irinotecan injection [43]. There are few studies which have shown direct influence of intestinal microbiota on the pathogenesis of irinotecan-induced mucositis [44,45]. Patient data has shown that there is a link between irinotecan metabolism, GUS and gut microbiome signatures in individual patients [46]. It has been shown that differences in gut microflora composition can lead to variability in GUS catalytic activity and inhibition potential.

Although, studies indicate strongly the direct role of GUS [47,48] relationship between GUS activity and mucositis is still controversial. In a study by Pedroso et al. *E. coli* producing GUS was found to have a direct relationship with the increase of intestinal permeability with irinotecan, but any recruitment of neutrophils and eosinophils, nor were histology changes observed. Moreover, antibiotic treatment improved irinotecan-induced mucositis in Gunn rats (animals have an inherent deficiency in the *UGT1A1* enzyme) [49] and a specific GUS inhibitor (D-saccharic acid 1.4-lactone) failed to alleviate diarrhea with irinotecan [50]. Thus, indicating involvement of possible mechanisms other than GUS.

Irinotecan is known to cause injury to the tight junction leading to BT in rats, [51] BT is the passage of viable bacteria and endotoxins from gastrointestinal to mesenteric lymph nodes (MLN), bloodstream, and other organs [52]. The tight junction of the intestinal epithelial barrier is essential in preventing BT [53]. Evidence is increasing that the intestinal microbiota plays a critical role in modulating the efficacy and toxicity of chemotherapeutic agents. The microbiota provides their host with metabolic capabilities [54]. Variation of microbiota may cause mucositis and sepsis [51,55].

Diarrhea attenuation through modulating gut microbiome: The intestinal microbiota are thus potential targets to improve the therapeutic efficacy and mitigate the toxicity of irinotecan. Current tools designed to manipulate the gut microbiota include dietary intervention with glutamine, probiotics, or non-digestible carbohydrates to protect epithelia barrier [56-58]. Another approach is to co-administer with antibiotics to decrease the level of microbiota and decrease the activity of GUS to alleviate chemotoxicity [59,60]. Amoxapine, a known inhibitor of GUS, has been shown to suppress irinotecan induced diarrhea in a rat model [61]. The deeper understanding of the interactions between irinotecan, intestinal microbiota, and tumor is warranted to come up with new therapies and preventions to reduce adverse effects and improve therapeutic efficacy.

Limitations of current strategies being investigated to manage irinotecan gut toxicity: Various molecular and pharmacological approaches have been tested to alleviate irinotecan-induced diarrhea through reducing the intestinal accumulation of SN-38 including: 1) *UGT1A1* induction (e.g., phenobarbital) [62], 2) CEs inhibition (e.g., benzene sulfonamide) [63], 3) CYP3A4 induction (e.g., phenytoin, carbamazepine) [64], 4) GUS inhibition (e.g., baicalin, probiotics, antibiotics) [65-67], 5) Hepatic transporter inhibition (e.g., cyclosporine) [62,68-70], and binding SN-38 using absorbents (e.g., aluminum silicate clay, activated charcoal) [71,72]. Other approaches have also been evaluated to protect gut damage such as using anti-inflammatory agents (e.g., pentoxifylline, thalidomide, celecoxib, RDP58, etc.), antibiotics, probiotics, oxidative stress inhibitors, intestinal alkalization, and herbal medicines [13,65,73]. Despite encouraging results in animal models or small scale of clinical trials, diarrhea is still a challenge for irinotecan therapy. Therefore, there is a critical need for fully mechanism investigation and for effective approaches to solve this urgent problem.

Gut-liver axis and EHR of irinotecan

The concept of the gut-liver axis was initially demonstrated in alcohol induced liver disease (ALD). Studies in rat demonstrated that acute alcohol transiently increased systemic levels of gut-derived endotoxin and associated detrimental effect could be protected by antibiotics [74]. Tight junction prevents both bacteria and toxin in the intestinal lumen and from the paracellular space getting into deep tissues. Recent studies have shown that SN-38 damaged the tight junction proteins, claudin-1 and occludin to disrupt the intestinal barrier,[75] and increase permeability (Figure1). This results in the translocation of bacteria and bacterial products (such as lipopolysaccharide, LPS and unmethylated CpG containing DNA) from the gut lumen to the liver *via* the portal vein [76-78]. Recent studies have shown that SN-38 gut accumulation leads to disruption of the epithelial barrier promoting BT [51,79-81]. The transport of bacteria and bacterial products to the liver is known to induce hepatic inflammation including cytokines and other inflammatory markers [82-84]. We and others have shown that hepatic drug metabolizing enzymes and drug transporters are primarily reduced during inflammation [85-87]. Therefore, it is possible that SN-38 exposure to

the gut will be increased due to the effect of the gut-liver axis on the EHR of irinotecan caused by increased BT-mediated hepatic inflammation. This novel mechanism of irinotecan gut toxicity needs to be investigated further. The liver is exposed to both gut microbes and SN-38 from the gut through the portal vein. Gut microbial components can cause inflammation in the liver, however SN-38 by itself can also induced inflammatory pathways. Future studies need to be conducted to elucidate the mechanism of hepatic inflammation in the gut-liver axis during irinotecan treatment.

Clinical implications of bacterial translocation

The concept of BT being the key to the gut-liver-gut dysfunction is interesting and it provides a better understanding of irinotecan-induced diarrhea than the currently hypothesized mechanisms. There is evidence in humans of the potential for BT from injured intestinal mucosa [88,89]. Indirect evidence with irinotecan is provided by the GERCOR study. This was a trial in which patients were treated with FOLFIRI compared to FOLFOX6 for metastatic colorectal cancer. Interestingly in patients who were treated with FOLFIRI (which is an irinotecan-based regimen) as a first-line therapy, the rate of grade 3-4 neutropenia rate was 25%, whereas with the FOLFOX6 the rate was 44% [90]. So irinotecan was less myelosuppressive, however when looking at the grade 3-4 neutropenia rate was 7% for patients receiving FOLFIRI *vs* only 1% for patients receiving FOLFOX [91]. This evidence would seem to indicate that while it produces less severe neutropenia, irinotecan likely has increased the rate of BT due to the increase in neutropenic febrile episodes.

The above statement is dependent on the assumption that BT plays a role in febrile neutropenia and there is evidence that this is the case. A study in patents with febrile neutropenia episodes looked at endotoxin and CD14 as a marker. The data showed that CD14 was higher in patient in gram-negative *bacteremia* than in gram-positive *bacteremia*. And this pattern was observed in cases where there was neutropenic fever without cultures indicating more likely gram-negative *bacteremia.* This would again seem to indicate BT as a more likely source [92-98].

The evidence presented above does seem to indicate that BT is an issue with irinotecan. Therefore, studies looking at BT-mediated effects on irinotecan EHR and consequently enteric toxicity of irinotecan is interesting and could provide further targets for intervention and aid patients in tolerating the therapy better.

Future Research Needed

Despite ongoing studies, there are no effective medications to efficiently manage irinotecan-induced late-onset diarrhea in patients. The major impediment is the lack of comprehensive understanding of the mechanism of this gut toxicity. To date all research have focused on gut-specific factors such as enzymes, inflammation, microbiome, etc. in order to understand the mechanism of toxicity. Future research is needed to identify the role of BT on hepatic SN-38 detoxifying enzymes, and their role in exacerbating irinotecan gut toxicity. Future research will focus on understanding the novel cross-talk between the gut and liver in order to develop new approaches to reduce/prevent irinotecan-induced diarrhea in patients.

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