

Irinotecan-Induced Diarrhea During A Protracted Administration Schedule for Pediatric Sarcomas – Mechanisms and Clinical Applications

Jie Xu, Lu Xie, Xin Sun, and Wei Guo*

Peking University People's Hospital, No.11, Xizhimen Street, Beijing, China

*Corresponding author:

Wei Guo,
Peking University People's Hospital, No.11,
Xizhimen Street, Beijing, China, E
-mail: bonetumor@163.com

Received: 15 Sep 2022

Accepted: 01 Oct 2022

Published: 07 Oct 2022

J Short Name: COO

Copyright:

©2022 Wei Guo, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:

Wei Guo. Irinotecan-Induced Diarrhea During A Protracted Administration Schedule for Pediatric Sarcomas – Mechanisms and Clinical Applications. Clin Onco. 2022; 6(12): 1-8

Keywords:

Irinotecan; Diarrhea; Pediatric sarcoma; Protracted schedule

Authors Contribution: AC: Activated Charcoal; CASAD: Calcium aluminosilicate clay; CID: Chemotherapy Induced Diarrhea; COG: Children's Oncology Group; IID: Irinotecan-Induced Diarrhea; LAR: Long-Acting Release; MTD: Maximum Tolerance Dose; RCT: Randomized Placebo-Controlled Trial; SN38G: SN38-Glucuronide; SC: Sub Cutaneously; UGT1A1: Uridine Diphosphate Glucuronosyltransferase Family 1 Member A1; SN38: 7-Ethyl-10-Hydrox Ycamptothecin

1. Abstract

Irinotecan-induced diarrhea, especially delay-type diarrhea is the most common and dose-limiting side effect of irinotecan. Evidence has shown that antitumor activity of irinotecan is enhanced with longer duration and lower dose administration in pediatric sarcoma compared to a single higher dose in colorectal cancer. Poor compliance to comprehensive strategies in children, overlap of acute and delayed symptoms, prolonged administration period and poor general health status in heavily treated patients should be considered in the pediatric protracted schedule. In this review, we discuss the mechanisms and their possible clinical applications in the prophylaxis and management of irinotecan-induced diarrhea in protracted schedule for pediatric patients with sarcoma, and come up with a strategy for the management of diarrhea in these patients. Conclusion: No robust biomarker has been found in relation to diarrhea. Prophylactic use of Cephalosporins and early salvage treatment with intensive loperamide are required. Further aggressive therapy includes octreotide and/or racecadotril, fluid resuscitation, symptomatic and supportive therapy are essential in the management of diarrhea.

2. Introduction

Irinotecan, a camptothecin analogue, was initially approved by the US Food and Drug Administration for the treatment of colorectal cancer in 1996 at a single high-dose schedule [1]. Subsequently, clinicsfoncology.com

it has become increasingly important in the treatment of pediatric sarcomas, such as Ewing sarcoma or rhabdomyosarcoma by a protracted administration schedule [2, 3]. Its active metabolite, SN-38, mediates cytotoxicity by stabilizing the DNA topoisomerase I complex formed during DNA replication, preventing religation of DNA, and restricting the activity of the topoisomerase I enzyme. Regardless of its administration schedule, diarrhea, especially delay-type diarrhea is the most common and dose-limiting side effect of irinotecan, both in colorectal cancer [1] and sarcomas [3]. Compared with a single high-dose schedule in colon cancer, irinotecan-induced diarrhea (IID) in protracted schedule in pediatric sarcoma patients has its own features and should be properly managed to reduce the dose-limiting IID and optimize the irinotecan therapy. In this review, we discuss the mechanisms and their possible clinical applications in the management of IID in protracted schedule for pediatric patients with sarcoma, and come up with a strategy for the management of IID in these patients. Protracted irinotecan administration schedule for sarcomas Preclinical studies in rhabdomyosarcoma and pediatric brain tumor xenografts showed that the antitumor activity of irinotecan was enhanced with longer duration and lower dose administration compared to a single higher dose, which was consistent with its S-phase specific mechanism of action [4]. Based on this finding, Furman et al. [5]. Reported the first pediatric phase I clinical trial of irinotecan using a protracted 20 mg/m²/d D1-5×2w every-3-week schedule instead

of a single dose of 180 mg/m²/d given every-3-week as part of the FOLFIRI regimen in colon cancer [6]. Thereafter, the protracted administration schedule of irinotecan was widely adopted as a second line chemotherapy schedule in sarcoma patients, varying from 600 mg/m² every 3 weeks [7], 125 mg/m²/d weekly 4x every 6 weeks [8], 180 mg/m²/d D1-3 every 4 weeks, 20 mg/m²/d D1-5×2w every 3 weeks [3, 4, 9-13], to 50 mg/m²/d D1-5 every 3 weeks intravenously [12-14] or orally at a higher dose of 90 mg/m²/d in the most recent VOIT regimen [15, 16]. Although the 20 mg/m²/d D1-5×2w every-3-week schedule was used in the clinic, each of these schedules was demonstrated to be effective and safe, but no agreement was reached on which schedule was the best. The only prospective study to compare the 5d and 5d×2w regimens came from the Children's Oncology Group (COG) focusing on rhabdomyosarcoma, where no difference in efficacy and grade 3-4 adverse events was found between the two arms [17].

3. Irinotecan-Induced Diarrhea (IID)

Two types of diarrhea were observed after administration of irinotecan, namely acute diarrhea and delayed diarrhea. Immediate-onset acute diarrhea is defined as diarrhea occurring within 24 hours after receiving irinotecan and is usually caused by acute cholinergic properties and is often accompanied by other symptoms of cholinergic excess, such as abdominal cramping, rhinitis, lacrimation, and salivation; acute diarrhea can be successfully prevented with the prophylactic use of atropine [18]. Delayed-type diarrhea is defined as diarrhea occurring more than 24 hours after the initial administration of irinotecan. The delayed form usually peaks after about 11 days treatment [11, 12].

4. Pharmacokinetics and Mechanisms of IID

A protracted exposure to 7-ethyl-10-hydroxycamptothecin (SN38), an active metabolite of irinotecan which was approximately 100-

to 1,000-fold more active than the parent drug, has been noticed in phase I clinical study three weeks after irinotecan infusion [19, 20]. Enterohepatic recycling of the drug was confirmed afterwards. According to the pharmacokinetics data of the irinotecan-based regimen [19, 20], most tumor responses were achieved at the highest doses administered, indicating a dose-effect relationship for anti-cancer activity. The intensity of the major adverse effects encountered with this drug (e.g., neutropenia and diarrhea) also correlated with the exposure (area under the curve) to SN38 [19]. The pathophysiological mechanism of IID has been explored and well established in recent decades. Irinotecan is converted by carboxylesterase in the liver to SN38, which is subsequently glucuronidated by hepatic Uridine Diphosphate Glucuronosyltransferase Family 1 Member A1 (UGT1A1) to SN38-glucuronide (SN38G) [21]. The variant of UGT1A1, which occurs in 10% of Caucasians, poorly metabolizes SN-38 and is thus an indicator of irinotecan toxicity, due to the lower excretion of SN-38 from the body in its SN-38G form [22]. Most of the SN38, as well as SN38G, are excreted along with bile and eventually eliminated via the fecal route, but a certain amount of them can also be excreted in the urine [23]. In the intestinal lumen, SN38G can be converted back to SN38 by β -glucuronidases produced by enteric bacteria [24] and intestinal carboxylesterases [25]. Active SN38 in the intestinal lumen causes direct damage to the intestinal mucosa and subsequently delayed diarrhea. The mechanisms of mucosal damage include excessive mucous secretion, water and electrolyte malabsorption [26], increased apoptosis, villous atrophy, crypt hypoplasia and dilation [27]. On the other hand, the luminal environment is altered by active local SN38, change of the bacterial genera, which favor those β -glucuronidases producing organisms as a positive feedback and thus exacerbate mucosa damage [28, 29] (Figure 1).

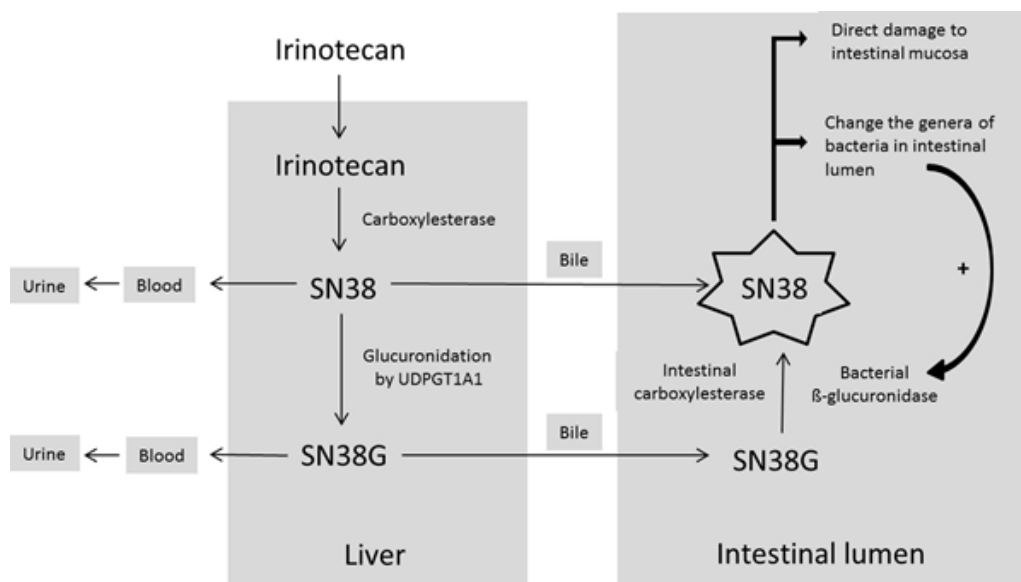


Figure 1: The pathophysiological mechanism of IID was described in figure 1.

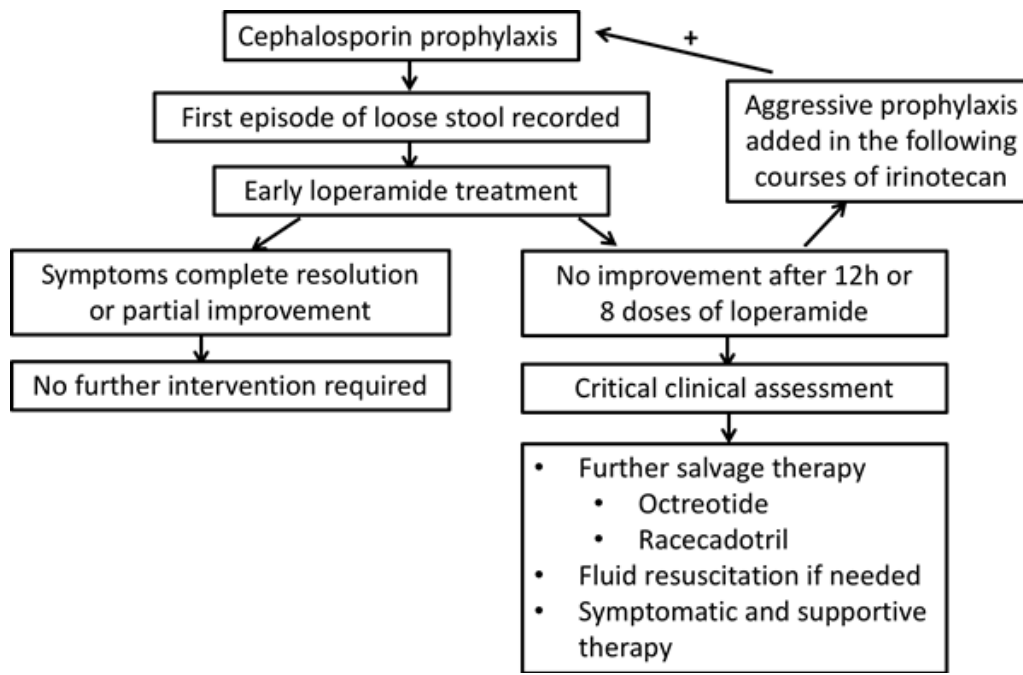


Figure 2: Recommended treatment for the management of IID in protracted schedule for pediatric sarcoma patients is depicted as a flowchart in figure 2.

5. Characteristics of IID in Protracted Schedule for Pediatric Sarcomas

As mentioned above, the protracted irinotecan administration schedule is widely adopted for pediatric patients with sarcoma. Data related to IID from studies using protracted irinotecan-based regimen in pediatric sarcomas are listed in Table S1A. Considering the rarity of pediatric sarcoma, the results from Phase 2 trials in pediatric brain tumors, where protracted irinotecan-based regimen also play an important role, were also reviewed (Table S1B) to obtain more information on IID in children. Compared with IID in metastatic colorectal cancer where a single dose is commonly used, IID in a protracted schedule has its own characteristics and is even more difficult to manage in the case of prolonged exposure. First, in the 5-day or 5-day weekly continuous schedule, an overlap of acute and delayed diarrhea requires special attention. Loose stool, an increase frequency of defecation and abdominal pain might be recognized as the early symptoms of both acute and delayed IID. However, while the acute form of IID can be easily controlled or prevented by atropine, the delayed IID must be treated as soon as possible. Once delayed IID is fulminant, salvage therapy is rarely successful even when a combination of several drugs is given [23, 30, 31]. Second, a prolonged period of time with the risk of IID should be considered when prophylaxis strategy is used. For example, given the positive feedback of the contribution of intestinal bacteria to IID [29], antibiotics such as cephalosporin to eliminate those microorganisms producing β -glucuronidases and

reduce biliary excretion of SN38 are widely used as a prophylactic measure. Although no agreement has been reached on the starting time of antibiotics prophylaxis, the first dose of antibiotics is commonly given 3-5 days prior to, and continued until 3 days after the irinotecan exposure [32-34], which may lead to the continuous oral or intravenous use of antibiotics in a 5d \times 2w schedule. The risk of antibiotics resistant bacterial infections as well as *C. difficile* enteritis afterwards should be taken into consideration. Third, the majority of patients with sarcoma, especially rhabdomyosarcoma and Ewing sarcoma where irinotecan-based regimen is most promising, are children and teenagers [9, 35]. Young patients are more likely to have poor compliance to continuous oral tablets use and other comprehensive strategies, such as monitoring and adjustment of the stool pH. Furthermore, nausea and vomit caused by chemotherapy could limit the oral administration of loperamide. The feasibility of approaches over a relatively long period of time should be assessed judiciously. Fourth, an irinotecan-based protracted regimen is often administered as second-line chemotherapy for most Ewing sarcoma patients and some rhabdomyosarcoma patients. These patients had been previously treated with a high dose of doxorubicin and/or alkylating agents, which resulted in poor general health, made them more fragile to cytotoxic drugs, and put them at a higher risk of myelosuppression [8, 36]. As another common adverse effect of irinotecan, myelosuppression could occur together with diarrhea. The co-occurrence of infection and IID makes it more difficult to manage it.

Table S1A: Diarrhea reported in studies using protracted irinotecan-base regimen in pediatric sarcoma patients.

Year	Author	Study	N(patients/ courses)	Protocol	Prophylaxis	Diarrhea (%Courses)		Diarrhea (%Patients)	
						Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
1999	Furman WL [1]	Phase 1	23/84	Irinotecan 20-29mg/m ² /d D ₁₋₅ ×2w every 3 weeks	None	NA	NA	57%	39%
2001	Blaney S [2]	Phase 1	35	Irinotecan 30-65mg/ m ² /d D ₁₋₅ every 3 weeks	None	NA	NA	40%	11%
2002	Cosetti M [3]	prospected	22	Irinotecan 20mg/m ² /d D ₁₋₅ ×2w, every 3 weeks	None	NA	NA	55%	18%
2002	Mugishima H [4]	Phase 1	28/51	Irinotecan 60-200 mg/m ² /d D ₁₋₃ every 4 weeks	None	NA	12%	NA	NA
2006	Shitara T [5]	prospected	16/32	Irinotecan 180 mg/m ² /d D ₁₋₃ every 4 weeks	None	56%	34%	NA ^a	NA
2006	Bisogno G [6]	Phase 2	32/79	Irinotecan 20mg/m ² /d D ₁₋₅ ×2w every 3 weeks	None	58%	11%	NA	NA
2007	Wagner LM [7]	prospective	16/95	Irinotecan 10-20mg/m ² /d D ₁₋₅ ×2w TMZ 100mg/m/d D ₁₋₅ every 3-4 weeks	5 patients received cephalosporin	NA	11%	NA	31%
2007	Pappo AS [8]	Phase 2	69/138	A: Irinotecan 20mg/m ² /d D ₁₋₅ , w _{0,1,3,4} B: Irinotecan 20mg/m ² /d D ₁₋₅ w _{0,1,3,4} VCR ^e 1.5mg/m ² w _{0,1,3,4}	2 patients with cefixime ^d	NA	A: 5% B: 22%	NA	NA
2007	Bomgaars LR [9]	Phase 2	171/634	Irinotecan 50mg/m ² /d D ₁₋₅ every 3 weeks	None	16% ≥grade2	NA	NA	
2009	Casey DA [10]	retrospective	20/154	Irinotecan 20mg/m ² /d D ₁₋₅ ×2w TMZ ^b 100mg/ m ² /d D ₁₋₅ , every 3 weeks	Cefixime	NA	5%	NA	NA
2009	Arceci RJ [11]	Phase 1	48	Cetuximab 75-250mg/m ² weekly Irinotecan 16mg/m ² /d D ₁₋₅ ×2w (pediatric) or 20mg/m ² /d D ₁₋₅ ×2w (adolescent) every 3 weeks	None	NA	NA	61%	24%
2010	Wagner LM [12]	Phase 1	42/56(A) +72(B)	A: Irinotecan 35-50mg/m ² /d D _{1-5, 8-12} TMZ 100-150mg/m ² /d D ₁₋₅ VCR 1.5 mg/m ² D _{1,8} every 3 weeks B: Irinotecan 70-90mg/m ² /d D ₁₋₅ TMZ 100-150mg/m ² /d D ₁₋₅ VCR 1.5 mg/m ² D ₁ every 3 weeks	Cefixime	A: 23% B: 17%	A: 5% B: 1%	NA	NA
2010	Mascarenhas L [13]	Phase 2	89	A: Irinotecan 20mg/m ² /d D ₁₋₅ , w _{1, 2, 4, 5} VCR 1.5 mg/m ² D ₁ w _{1, 2, 4, 5} B: Irinotecan 20mg/m ² /d D ₁₋₅ , w _{1, 4} VCR 1.5 mg/m ² D ₁ w _{1, 2, 4, 5}	None	A: 22% B: 13%		NA	NA
2013	Wagner L [14]	Pilot study	13/36	VCR 1.5 mg/m ² D ₁ Irinotecan 90 mg/m ² /d D ₁₋₅ po TMZ 100-150 mg/ m ² /d D ₁₋₅ Bevacizumab 15 mg/kg D ₁ every 3 weeks	Cefixime	NA	NA	NA	8%
2013	Venkatramani R [15]	Phase 1	12/87	VCR 1.5 mg/m ² D _{1,8} Irinotecan 30-50 mg/m ² /d D ₁₋₅ iv TMZ 100 mg/ m ² /d D ₁₋₅ Bevacizumab 15 mg/kg D ₁ every 3 weeks	Cefixime or Cefpodoxime ^c	69%	1%	NA	NA
2014	Bagatell R [16]	Phase 1 solid tumor	71/280	TEM ^f 15-35 mg/m ² D _{1,8} VCR 1.5 mg/m ² D _{1,8} Irinotecan 50-90 mg/m ² /d D ₁₋₅ po TMZ 100-150 mg/ m ² /d D ₁₋₅ every 3 weeks	Cefixime or equivalent	Grade 2 4%	1%	NA	NA

2014	Brennan RC [17]	Phase 1	16/32	Irinotecan 50mg/m ² /d D _{1-5,8-12} po Gefitinib 150 mg/ m ² /d D ₁₋₁₂ every 3 weeks	Cefixime or Cefpodoxime ^e	NA	16%	NA	NA
2015	Kurucu N [18]	retrospective	20/97	Irinotecan 20mg/m ² /d D ₁₋₅ × 2w TMZb 100mg/ m ² /d D ₁₋₅ , every 3 weeks	None	NA	NA	NA	9.2%
2016	Weigel BJ [19]	Phase 2 RMS	109	In VDC/IE/VI ^g Irinotecan 20mg/m ² /d D ₁₋₅ × 2w. When the results of COG ARST0121 demonstrated shorter schedule was equivalent schedule, the study was amended to use the shorter d × 5 schedule (50mg/m ² /d D ₁₋₅).	None	NA	NA	NA	18-20%

Table S1: Diarrhea reported in Phase 2 trials using protracted irinotecan-base regimen for pediatric brain tumors.

Year	Author	Diagnosis	N(patients/courses)	Protocol	Prophylaxis	Diarrhea (%Courses)		Diarrhea (%Patients)	
						Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
2013	Hargrave D [20]	Glioma	17/34	TMZ 100 mg/ m ² /d D ₁₋₅ Irinotecan 10 mg/m ² /d D _{1-5,8-12} every 3 weeks	None	NA	NA	59%	0
2013	Grill J [21]	Medulloblastoma	66	Irinotecan 10 mg/m ² /d D _{1-5,8-12} TMZ 100-125 mg/m ² /d D ₁₋₅ every 3 weeks	None	NA	NA	52%	8%
2017	Mody R [22]	Neuroblastoma	35	VCR 1.5 mg/m ² D _{1,8} Irinotecan 50 mg/m ² /d D ₁₋₅ TMZ 100 mg/ m ² /d D ₁₋₅ every 3 weeks A: TEM 35 mg/m ² /d D _{1,8} B: Dinutuximab 17.5 mg/m ² /d or 25 mg/m ² /d D ₂₋₅	Cefixime or equivalent ^h	NA	NA	NA	9%
2017	Modak S [23]	Neuroblastoma	33	Bevacizumab 15mg/kg D _{1,15} Irinotecan 50 mg/m ² /d D _{4,8} TMZ 100 mg/m ² /d D _{4,8} every 3 weeks	Cefixime or equivalent ^h	NA	NA	79%	3%

^a NA: not available

^b TMZ: Temozolomide

^c: VCR: Vincristine

^d: No diarrhea was recorded in the 2 patients with cefixime prophylaxis.

^e: Prophylaxis was given if grade 3 diarrhea was observed previously.

^f: TEM: temsirolimus

^g: VDC/IE/VI: V, vincristine; D, doxorubicin; C, cyclophosphamide; IE, ifosfamide + etoposide; VI, vincristine + irinotecan

^h: Prophylactic use was permitted but not mandatory.

6. Possible Clinical Applications

6.1. Risk Assessment

Given the rarity of sarcoma, most evidence on predictors of IID came from colorectal cancer. The main clinical predictors are weekly administration, poor performance status, high serum creatinine levels, prior abdominopelvic irradiation, low leukocyte counts, age over 70 years, UGT1A1*28 polymorphism (Gilbert syndrome) and Crigler-Najjar syndrome type I[37]. Considering the early-onset of sarcoma where a protracted schedule is applicable, the general status including basic functions of the major

organs, and the UGT1A1 (key enzyme in the glucuronidation of SN38 in the liver) genotype are two major factors used to assess the risk of IID. However, although agreement has been reached in the predictive value of the UGT1A1 genotype in colorectal cancer, where single high-dose irinotecan is adopted[38-40], its value in a low-dose protracted schedule remains insignificant based on two phase 2 clinical trials[41] and a phase I clinical trial from the COG [42]. As a result, the detection of the UGT1A1 genotype is not typically recommended in protracted schedules in pediatric patients. Unfortunately, no other genetic markers have been found for this group.

7. Drugs Used in the Management of IID

Although strategies that might reduce the rate of conversion of SN-38G to SN-38, such as intestinal alkalization, anticyclo-oxygenase 2 therapy, probiotics, antibiotics, and absorbing agents, have shown no benefits [43].

8. Prophylactic Therapy

8.1. Antibiotics

Aerobic bacteria comprise less than 1% of the normal GI flora. Among them, *Escherichia coli* and other Gram-negative bacteria are the principal producers of beta-glucuronidase. The use of antibiotics to eliminate these bacteria in the gut and reduce the enterohepatic recycling of glucuronide-conjugated drugs to prevent the conversion of SN38G to active SN38 has been adopted as a preventative and also salvage methods in IID. Neomycin was the first antibiotics used as an effective prophylaxis in 2001[44]. The combination of neomycin with loperamide [45] or bacitracin[46] as secondary prophylaxis was demonstrated in trials with a small sample size. However, they failed in a multicenter, double-blind, randomized, placebo-controlled trial (RCT). Moreover, a higher risk of nausea was recorded in the neomycin arm [47]. Ciprofloxacin, enoxacin and gatifloxacin significantly decreased SN38G deconjugation and, thus SN-38 formation, which was not observed with levofloxacin, streptomycin, ampicillin and amoxicillin/clavulanate [48]. Since an increased risk of arthropathy was recognized in juvenile animals, the use of fluoroquinolones is limited in pediatric patients. Third-generation cephalosporins have a broad spectrum of activity, good palatability and further increased activity against gram-negative organisms. A phase 1 study in pediatric solid tumors showed that cefixime administered with oral irinotecan (5d×2w every-3-week) was well tolerated in children, significantly reduced beta-glucuronidase activity in the evaluated stools, and allowed greater dose escalation of irinotecan [49]. An increase of 50% in the maximum tolerance dose (MTD) of intravenous irinotecan administered with a protracted schedule [50] was also achieved with the help of cefpodoxime. Cefixime prophylaxis at a dose of 8 mg/kg/d (maximum dose of 400 mg) or cefpodoxime prophylaxis at a dose of 10 mg/kg/day twice daily (maximum dose 400 mg/d) beginning 2 or 5 days before irinotecan administration and continuing throughout the course the treatment was then used in the following several protracted pediatric studies [15,16,42,51,52]. A lower occurrence of diarrhea was noticed with the prophylactic use of cephalosporins in these studies (Table S1A-B). Grade 3 diarrhea was observed in only 7-14% of all evaluable patients, and no grade 4 diarrhea was seen. More robust evidence was revealed by the finding that the proportion of diarrhea decreased from 76% of the courses (7% grade 3) to 48% of the courses (2% grade 3) after cephalosporin prophylaxis was implemented in the same study [52]. Although fungal overgrowth, *C difficile* enteritis and antibiotic-induced diarrhea resulting from long-term antibiotic use should always be considered, no compli-

cations attributed to cephalosporin prophylaxis have been reported to date. Based on these findings, cephalosporin prophylaxis is adopted in most protracted studies in COG thereafter. Cefixime and cefpodoxime has a similar range of antibacterial activity. Thus, the choice of different third-generation cephalosporins is typically based on clinical convenience.

9. Probiotics

Probiotic bacteria reduce the activity of intestinal beta-glucuronidase, and therefore these bacteria could be used in the prevention of IID [53, 54]. In 2015, a randomized double blind, placebo controlled pilot study in colon cancer revealed that probiotics administered orally, at a dose of 10×10^9 CFU of bacteria, three times daily for 12 weeks of chemotherapy led to a reduction in the incidence of severe diarrhea of grade 3 or 4 (0% for probiotics vs. 17.4% for placebo, $p=0.11$)[55]. To the best of our knowledge, no data on protracted irinotecan-based schedule in pediatric patients has been reported.

10. Activated Charcoal

Activated charcoal (AC) has a documented history of its ability to attract and expel ingested toxins from the gastrointestinal tract. According to a systematic review published in 2018 focusing on AC in the management of diarrhea [56], it acts to prevent system absorption of these adverse agents, adsorbing them on the surface of its particles, which makes AC a suitable diarrheal treatment with exceptionally few side-effects. A prospective study in 22 pediatric patients using irinotecan-based regimen showed that with the prophylaxis of AC at a dose of 250 mg three times daily, the occurrence of grade 3 and 4 diarrhea was reduced from 52.3% in the placebo group to 6.6% in the experimental group[57]. A similar positive result was reported in adults receiving single high-dose irinotecan [58]. Based on these data, prophylactic AC may have a role in reducing the dose-limiting IID and optimizing irinotecan therapy.

11. Bowel Alkalinization

Under acidic conditions, irinotecan and its active metabolite SN-38 exist preferably as the lactone form, whereas under basic conditions both exist as the carboxylate form. The intestinal uptake rate of both forms appears to be pH-sensitive under physiological conditions. A study in Japan showed that intestinal alkalization was effective in preventing IID, however, the plasma levels of irinotecan and SN38 were significantly decreased as a result of altered pharmacokinetics, challenging the efficacy of the chemotherapy [59]. In addition, previously reported intestinal alkalization involved oral administration of 4 doses per day of 0.5 g of each sodium bicarbonate and magnesium oxide, 3 doses per day of 100 mg of ursodeoxycholic acid, and basic water (pH greater than 7.2) continuously for a total of 1,500 to 2,000 mL per day [60, 61]. However, the feasibility of such a comprehensive protocol is limited in pediatric patients.

12. Other Drugs as Prophylaxis

Many other drugs with different mechanisms have been reported in case reports or preclinical animal models, showing efficacy in the prevention of IID, including the Chinese herb Hange-Shashito (TJ-14), which acts as a natural inhibitor of the β -glucuronidase activity in bacterial microflora [62]; cyclooxygenase-2 inhibitors, such as celecoxib [63]; probenecid, which acts as a biliary inhibitor of CPT-11 and SN-38 secretion [64]; chrysin, which shifts the SN-38G/SN-38 equilibrium towards the inactive SN-38G in the gastrointestinal mucosa by upregulating the expression of UGT1A1 [65]; thalidomide whose mechanism is unclear [66, 67]; oral glutamine supplement [68-70]; calcium aluminosilicate clay (CASAD), as a naturally occurring clay that serves as a cation exchange absorbent [71]. Further prospective randomized studies are needed to definitively confirm these findings, especially in pediatric patients considering their feasibility and clinical convenience.

13. Salvage Therapy

13.1. Loperamide

Loperamide (an opioid) is the most commonly used drug in chemotherapy induced diarrhea (CID). It functions as an agonist to opioid receptors (present within the gastrointestinal tract), slows gut peristalsis, increases gut transit time and promotes fluid reabsorption [72]. Loperamide is not absorbed into the body and is excreted in the feces and the risk of overdose in this clinical setting is unlikely. According to the guidance on the management of diarrhea during chemotherapy published in 2014 in *Lancet Oncology*, patients with IID regardless of grades should start self-medicating with 4 mg loperamide followed by 2 mg up to every 2 h as a first-line therapy after an episode of diarrhea [43]. In pediatric patients, the recommended dose of loperamide by the COG and FDA is listed in Table 1 [15, 42, 73]. Taking it 30 min before food is recommended if the patients can still eat to make it more effective [73-75]. Patients could stop loperamide only after being diarrhea free for ≥ 12 h [73]. If no improvement was observed after 12 h or eight doses of loperamide, further assessment and more aggressive salvage therapy should be taken.

14. Octreotide

Octreotide is a synthetic somatostatin analogue that decreases hormone secretion (e.g., vasoactive intestinal polypeptide), reduces motility and pancreatic secretions and increases water absorption to control diarrhea as well as carcinoid-syndrome symptoms. In the treatment of CID, both therapeutic and prophylactic uses have been reported. In a meta-analysis of RCTs comparing the use of octreotide versus placebo in 2014 including 572 patients, the significant efficacy of octreotide compared with the placebo (OR, 4.9; 95% CI, 1.58-15.2) was confirmed [76]. In a subsequent subgroup analysis, even more benefit was revealed in the therapeutic subgroup (OR, 7.30; 95% CI, 4.09-13.04) rather than the prophylactic subgroup (OR, 2.11; 95% CI, 0.51-2.89). As a prophylaxis, a

randomized phase 3 trial exploring the use of long-acting release (LAR) octreotide in the prevention of CID in colorectal cancer (the LARCID trial) failed to demonstrate any benefit from octreotide LAR in terms of need for diarrhea treatment, opioids, or intravenous hydration or in the rate of hospitalization or quality of life [77]. Dose recommendation is 100 μ g three times daily; increase if no improvement is observed after 24 h (maximum 500 μ g per day) for intractable diarrhea; in severely ill patients start at 500 μ g three times daily) [43]. In pediatric patients, few robust evidence focusing on the treatment of CID has been reported. A significant reduction of stool output has been recognized in a retrospective study in pediatric patients at doses ranging from 8 to 60 μ g/kg/d subcutaneously (SC) twice or three times daily [78].

15. Racecadotril

Racecadotril (acetorphan) acts as a peripherally acting enkephalinase inhibitor. Unlike other opioid medications, such as loperamide, which reduce intestinal motility, racecadotril has an anti-secretory effect, reducing the secretion of water and electrolytes into the intestine [79]. According to a meta-analysis of RCTs summarizing the evidence on racecadotril compared with placebo or other interventions for the treatment of acute diarrhea in children published in 2016, racecadotril appears to be safe and well-tolerated, but the evidence of efficacy is limited due to sparse data, heterogeneity and risk of bias [80]. Additionally, no evidence on CID was found. A comparison study in adults suggested that the combination of racecadotril and loperamide may be more effective than either drug alone [23]. A dose of 1.5 mg/kg/dose three times daily is recommended [80, 81]. Recommended strategy for management of IID in protracted schedule for pediatric sarcoma patients Base on the above evidence, our recommended treatment for the management of IID in protracted schedule for pediatric sarcoma patients is depicted as a flowchart in Fig.2. First, we concur that all pediatric patients planning to receive a protracted irinotecan-based regimen should take mandatory cephalosporin prophylaxis, either cefixime at a dose of 8 mg/kg/d (maximum dose 400 mg) or cefpodoxime a dose of 10 mg/kg/day divided twice daily (maximum dose 400 mg/d) beginning 3 days before irinotecan and continuing throughout the course of the treatment. Second, early intervention of diarrhea is required once the first episode of loose stool is recorded. The initial treatment of IID is loperamide based on the weight of the patients (Table 1). If all symptoms are completely or partially resolved, no further intervention is required. If the patients do not respond to loperamide and no improvement is observed after 12 h or eight doses of loperamide, critical clinical reassessment is suggested and further aggressive salvage therapy is needed, such as octreotide and/or racecadotril. Always keep in mind that fluid resuscitation, symptomatic and supportive therapy are essential in the management of diarrhea. In the subsequent courses of irinotecan, more prophylaxis such as activated charcoal and probiotics could be induced to prevent IID.

Table 1: Dose recommendation of loperamide for pediatric patients.

Weight	First dose	Subsequent dose	During night
>43kg	4 teaspoonfuls ^a or 2 caplets ^b	1 teaspoonful or 1 caplet every 2h	2 caplets every 4h
30-43kg	2 teaspoonfuls or 1 caplet	1 teaspoonful or 1/2 caplet every 2h	1 caplet every 4h
20-30kg	2 teaspoonfuls or 1 caplet	1 teaspoonful or 1/2 caplet every 3h	1 caplet every 4h
13-20kg	1 teaspoonful	1 teaspoonful every 3h	1 teaspoonful every 4h
<13kg	1/2 teaspoonful	1/2 teaspoonful every 3h	1/2 teaspoonful every 4h

^aEach 7.5mL (1 ½ teaspoonful) contains loperamide 1mg.

^bEach caplet contains loperamide 2mg.

References

- Furman WL, Stewart CF, Poquette CA, Pratt CB, Santana VM, Zamboni WC, et al.. Direct translation of a protracted irinotecan schedule from a xenograft model to a phase I trial in children. *J Clin Oncol.* 1999; 17: 1815-24.
- Blaney S, Berg SL, Pratt C, Weitman S, Sullivan J, Luchtman-Jones L, et al. A phase I study of irinotecan in pediatric patients: a pediatric oncology group study. *Clin Cancer Res.* 2001; 7: 32-7.
- Cosetti M. Irinotecan for pediatric solid tumors: The Memorial Sloan-Kettering experience. *J Pediatr Hematol Oncol.* 2002; 24: 101-5.
- Mugishima H. Phase I study of irinotecan in pediatric patients with malignant solid tumors. *J Pediatr Hematol Oncol.* 2002; 24: 94-100.
- Shitara T. Irinotecan for children with relapsed solid tumors. *Pediatr Hematol Oncol.* 2006; 23: 103-10.
- Bisogno G. Phase II study of a protracted irinotecan schedule in children with refractory or recurrent soft tissue sarcoma. *Cancer.* 2006; 106: 703-7.
- Wagner LM. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. *Pediatr Blood Cancer.* 2007; 48: 132-9.
- Pappo AS. Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: The Children's Oncology Group. *J Clin Oncol.* 2007; 25: 362-9.
- Bomgaars LR. Phase II trial of irinotecan in children with refractory solid tumors: A Children's Oncology Group Study. *J Clin Oncol.* 2007; 25: 4622-7.
- Casey DA. Irinotecan and temozolomide for Ewing sarcoma: The Memorial Sloan-Kettering experience. *Pediatr Blood Cancer.* 2009; 53: 1029-34.
- Trippett TM. Phase I and pharmacokinetic study of cetuximab and irinotecan in children with refractory solid tumors: a study of the pediatric oncology experimental therapeutic investigators' consortium. *J Clin Oncol.* 2009; 27: 5102-8.
- Wagner LM. Phase I trial of two schedules of vincristine, oral irinotecan, and temozolomide (VOIT) for children with relapsed or refractory solid tumors: A Children's Oncology Group phase I consortium study. *Pediatr Blood Cancer.* 2010; 54: 538-45.
- Mascarenhas L. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2010; 28: 4658-63.
- Wagner L, Turpin B, Nagarajan R, Weiss B, Cripe T, Geller J, et al. Pilot study of vincristine, oral irinotecan, and temozolomide (VOIT regimen) combined with bevacizumab in pediatric patients with recurrent solid tumors or brain tumors. *Pediatr Blood Cancer.* 2013; 60: 1447-51.
- Venkatramani R, Malogolowkin M, Davidson TB, May W, Sposto R, Mascarenhas L, et al. A phase I study of vincristine, irinotecan, temozolomide and bevacizumab (vitb) in pediatric patients with relapsed solid tumors. *PLoS One.* 2013; 8: 68416.
- Bagatell R. Phase 1 trial of temsirolimus in combination with irinotecan and temozolomide in children, adolescents and young adults with relapsed or refractory solid tumors: A Children's Oncology Group Study. *Pediatr Blood Cancer.* 2014; 61: 833-9.
- Brennan RC. Phase I dose escalation and pharmacokinetic study of oral gefitinib and irinotecan in children with refractory solid tumors. *Cancer Chemother Pharmacol.* 2014; 74: 1191-8.
- Kurucu N, Sari N, Ilhan IE. Irinotecan and temozolamide treatment for relapsed Ewing sarcoma: a single-center experience and review of the literature. *Pediatr Hematol Oncol.* 2015; 32: 50-9.
- Weigel BJ. Intensive Multiagent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide and Vincristine/Doxorubicin/Cyclophosphamide, Irinotecan, and Radiation, in Patients with High-Risk Rhabdomyosarcoma: A Report from the Children's Oncology Group. *J Clin Oncol.* 2016; 34: 117-22.
- Hargrave D. A phase II single-arm study of irinotecan in combination with temozolomide (TEMIRI) in children with newly diagnosed high grade glioma: a joint ITCC and SIOPE-brain tumour study. *J Neurooncol.* 2013; 113: 127-34.
- Grill J. Phase II study of irinotecan in combination with temozolomide (TEMIRI) in children with recurrent or refractory medulloblastoma: a joint ITCC and SIOPE brain tumor study. *Neuro Oncol.* 2013; 15: 1236-43.
- Mody R, Naranjo A, Van Ryn C, Yu AL, London WB, Shulkin BL, et al. Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. *Lancet Oncol.* 2017; 18: 946-57.
- Modak S, Kushner BH, Basu E, Roberts SS, Cheung NK. Combination of bevacizumab, irinotecan, and temozolomide for refractory or relapsed neuroblastoma: Results of a phase II study. *Pediatr Blood Cancer.* 2017; 64.