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Irinotecan-Induced Diarrhea during a Protracted Administration Schedule for Pediatric Sarcomas - Mechanisms and Clinical Applications

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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.

Keywords: Irinotecan; Diarrhea; Pediatric sarcoma; Protracted schedule

Abbreviations

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: Subcutaneously; UGT1A1: Uridine Diphosphate Glucuronosyltransferase Family 1 Member A1; SN38: 7-ethyl-10-Hydroxycamptothecin

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, 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

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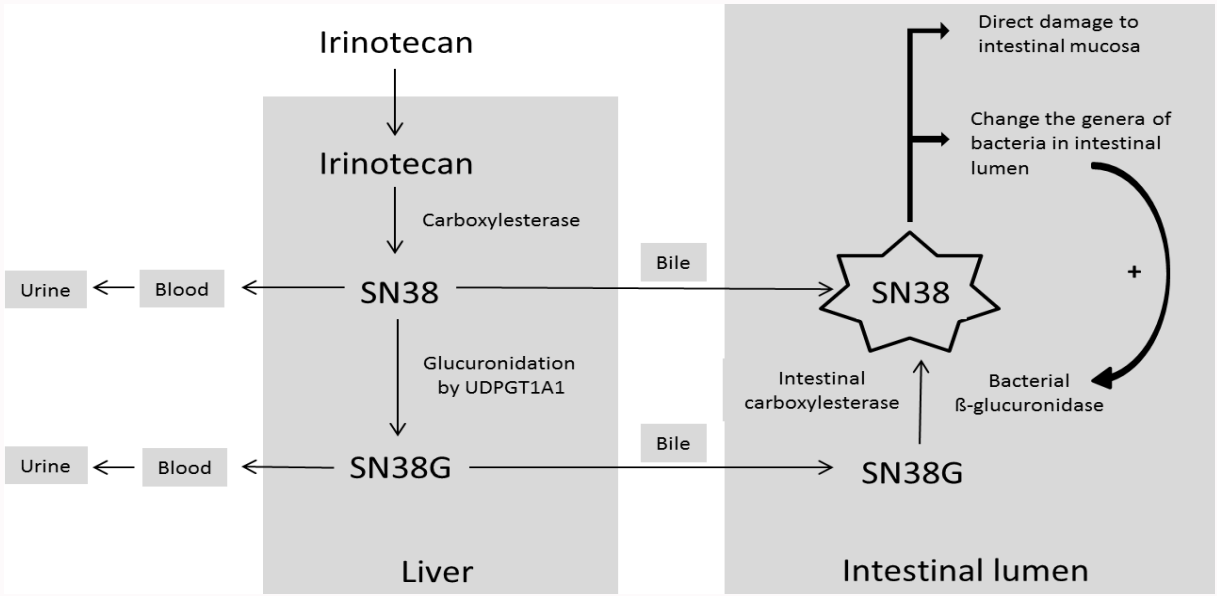

Figure 1: The pathophysiological mechanism of IID was described.

of irinotecan using a protracted 20 mg/m^2/d $D_{1\text{-}5}$ × 2 w every-3-week schedules instead of a single dose of 180 mg/m^2/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/m^2 every 3 weeks [7], 125 mg/m^2/d weekly 4x every 6 weeks [8], 180 mg/m^2/d$D_{1\text{-}3}$ every 4 weeks, 20 mg/m^2/d $D_{1\text{-}5}$ × 2 w every 3 weeks [3,4,9-13], to 50 mg/m^2/d$D_{1\text{-}5}$ every 3 weeks intravenously [12-14] or orally at a higher dose of 90 mg/m^2/d in the most recent VOIT regimen [15,16]. Although the 20 mg/m^2/d $D_{1\text{-}5}$× 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].

Irinotecan-Induced Diarrhea (IID)

Two types of diarrheas were observed after administration of irinotecan, namely acute diarrhea and delayed diarrhea. Immediate-onset acute diarrhea is defined as diarrhea occurring within 24 h 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 h after the initial administration of irinotecan. The delayed form usually peaks after about 11 days treatment [11,12].

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 anticancer 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).

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 to obtain more information on IID in children (Table S1B). 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 to 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 × 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.

Possible Clinical Applications

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 1 [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.

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 alkalinization, anti-cyclooxygenase 2 therapy, probiotics, antibiotics, and absorbing agents, have shown no benefits [43].

Prophylactic Therapy

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 as secondary prophylaxis was demonstrated in trials with a small sample size [46]. 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 was also achieved with the help of cefpodoxime [50]. 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, S1B). Grade 3 diarrhea was observed in only 7% to 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

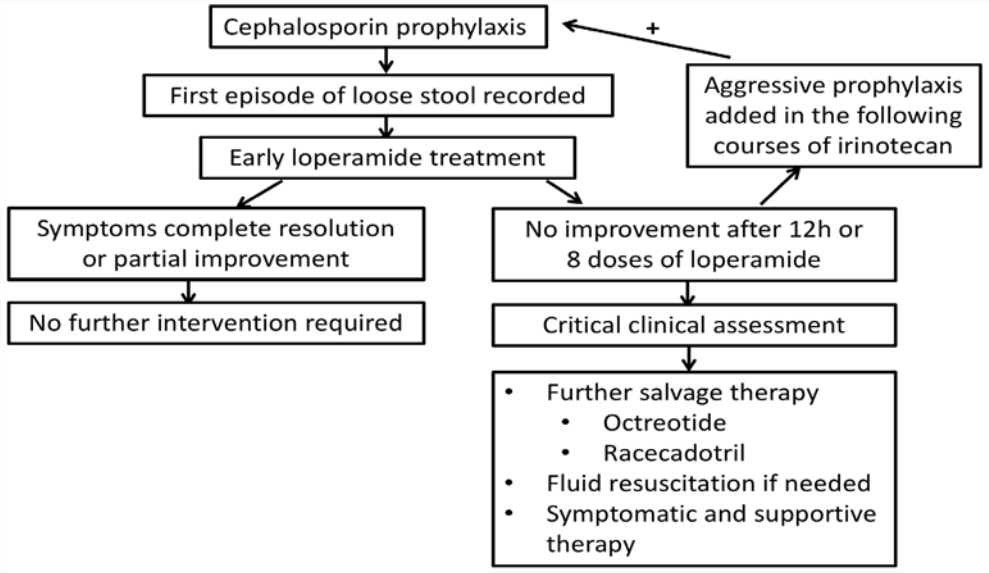

Figure 2: Recommended treatment for the management of IID in protracted schedule for pediatric sarcoma patients is depicted as a flowchart.

and antibiotic-induced diarrhea resulting from long-term antibiotic use should always be considered, no complications 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.

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.

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.

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 alkalinization 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 alkalinization 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.

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 inbacterial 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.

Salvage Therapy

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.

Table 1: Dose recommendation of loperamide for pediatric patients.

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

[a]Each 7.5 mL (1½ teaspoonful) contains loperamide 1 mg
[b]Each caplet contains loperamide 2 mg

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.

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 *vs.* 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 μg three times daily; increase if no improvement is observed after 24 h (maximum 500 μg per day) for intractable diarrhea; in severely ill patients start at 500 μg 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 μg/kg/d Subcutaneously (SC) twice or three times daily [78].

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 Figure 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 dp 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.

References

1. Ducreux M, Gil-Delgado M, André T, Ychou M, de Gramond A, Khayat D. [Irinotecan in combination for colon cancer]. Bull Cancer. 1998:43-6.
2. Shitara T, Shimada A, Hanada R, Matsunaga T, Kawa K, Mugishima H, et al. Irinotecan for children with relapsed solid tumors. Pediatr Hematol Oncol. 2006;23(2):103-10.
3. Cosetti M, Wexler LH, Calleja E, Trippett T, LaQuaglia M, Huvos AG, et al. Irinotecan for pediatric solid tumors: The Memorial Sloan-Kettering experience. J Pediatr Hematol Oncol. 2002;24(2):101-5.
4. Houghton PJ, Cheshire PJ, Hallman 2nd JD, Lutz L, Friedman HS, Danks MK, et al. Efficacy of topoisomerase I inhibitors, topotecan and irinotecan, administered at low dose levels in protracted schedules to mice bearing xenografts of human tumors. Cancer Chemother Pharmacol. 1995;36(5):393-403.
5. 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(6):1815-24.
6. Marques RP, Duarte GS, Sterrantino C, Pais HL, Quintela A, Martins AP, et al. Triplet (FOLFOXIRI) versus doublet (FOLFOX or FOLFIRI) backbone chemotherapy as first-line treatment of metastatic colorectal

cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;118:54-62.

7. Morland B, Platt K, Whelan JS. A phase II window study of irinotecan (CPT-11) in high-risk Ewing sarcoma: A Euro-E.W.I.N.G. study. Pediatr Blood Cancer. 2014;61(3):442-5.

8. Bomgaars L, Kerr J, Berg S, Kuttesch J, Klenke R, Blaney SM. A phase I study of irinotecan administered on a weekly schedule in pediatric patients. Pediatr Blood Cancer. 2006;46(1):50-5.

9. 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(1):50-9.

10. Casey DA, Wexler LH, Merchant MS, Chou AJ, Merola PR, Price AO, et al. Irinotecan and temozolomide for Ewing sarcoma: The Memorial Sloan-Kettering experience. Pediatr Blood Cancer. 2009;53(6):1029-34.

11. Wagner LM, McAllister N, Goldsby RE, Rausen AR, McNall-Knapp RY, McCarville MB, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer. 2007;48(2):132-9.

12. Pappo AS, Lyden E, Breitfeld P, Donaldson SS, Wiener E, Parham D, et al. 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(4):362-9.

13. Bisogno G, Riccardi R, Ruggiero A, Arcamone G, Prete A, Surico G, et al. Phase II study of a protracted irinotecan schedule in children with refractory or recurrent soft tissue sarcoma. Cancer. 2006;106(3):703-7.

14. Bomgaars LR, Bernstein M, Krailo M, Kadota R, Das S, Chen Z, et al. Phase II trial of irinotecan in children with refractory solid tumors: A Children's Oncology Group Study. J Clin Oncol. 2007;25(29):4622-7.

15. Wagner LM, Perentesis JP, Reid JM, Ames MM, Safgren SL, Nelson Jr MD, et al. 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(4):538-45.

16. Wagner L, Turpin B, Nagarajan R, Weiss B, Cripe T, Geller J. 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(9):1447-51.

17. Mascarenhas L, Lyden ER, Breitfeld PP, Walterhouse DO, Donaldson SS, Paidas CN, et al. 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(30):4658-63.

18. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: Pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010;2(1):51-63.

19. Chabot GG, Abigerges D, Catimel G, Culine S, de Forni M, Extra JM, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol. 1995;6(2):141-51.

20. Mathijssen RH, Verweij J, Loos WJ, de Bruijn P, Nooter K, Sparreboom A. Irinotecan pharmacokinetics-pharmacodynamics: The clinical relevance of prolonged exposure to SN-38. Br J Cancer. 2002;87(2):144-50.

21. Voigt W, Matsui S, Yin MB, Burhans WC, Minderman H, Rustum YM. Topoisomerase-I inhibitor SN-38 can induce DNA damage and chromosomal aberrations independent from DNA synthesis. Anticancer Res. 1998;18(5A):3499-505.

22. O'Dwyer PJ, Catalano RB. Uridine diphosphate Glucuronosyltransferase (UGT) 1A1 and irinotecan: Practical pharmacogenomics arrives in cancer therapy. J Clin Oncol. 2006;24(28):4534-8.

23. Saliba F, Hagipantelli R, Misset JL, Bastian G, Vassal G, Bonnay M, et al. Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: A prospective assessment. J Clin Oncol. 1998;16(8):2745-51.

24. Chu XY, Kato Y, Ueda K, Suzuki H, Niinuma K, Tyson CA, et al. Biliary excretion mechanism of CPT-11 and its metabolites in humans: Involvement of primary active transporters. Cancer Res. 1998;58(22):5137-43.

25. Khanna R, Morton CL, Danks MK, Potter PM. Proficient metabolism of irinotecan by a human intestinal carboxylesterase. Cancer Res. 2000;60(17):4725-8.

26. Takasuna K, Hagiwara T, Hirohashi M, Kato M, Nomura M, Nagai E, et al. Involvement of beta-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats. Cancer Res. 1996;56(16):3752-7.

27. Gibson RJ, Bowen JM, Inglis MRB, Cummins AG, Keefe DMK. Irinotecan causes severe small intestinal damage, as well as colonic damage, in the rat with implanted breast cancer. J Gastroenterol Hepatol. 2003;18(9):1095-100.

28. Takasuna K, Hagiwara T, Hirohashi M, Kato M, Nomura M, Nagai E, et al. Inhibition of intestinal microflora beta-glucuronidase modifies the distribution of the active metabolite of the antitumor agent, irinotecan hydrochloride (CPT-11) in rats. Cancer Chemother Pharmacol. 1998;42(4):280-6.

29. Stringer AM, Gibson RJ, Logan RM, Bowen JM, Yeoh ASJ, Keefe DMK. Faecal microflora and beta-glucuronidase expression are altered in an irinotecan-induced diarrhea model in rats. Cancer Biol Ther. 2008;7(12):1919-25.

30. Wadler S, Benson 3rd AB, Engelking C, Catalano R, Field M, Kornblau SM, et al. Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol. 1998;16(9):3169-78.

31. Benson AB 3rd, Ajani JA, Catalano RB, Engelking C, Kornblau SM, Martenson JA Jr, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918-26.

32. Middleton G, Brown S, Lowe C, Maughan T, Gwyther S, Oliver A, et al. A randomised phase III trial of the pharmacokinetic biomodulation of irinotecan using oral ciclosporin in advanced colorectal cancer: Results of the Panitumumab, Irinotecan & Ciclosporin in Colorectal cancer therapy trial (PICCOLO). Eur J Cancer. 2013;49(16):3507-16.

33. Nariai H, Shitara T, Oto Y, Natsumeda T, Taniuchi M, Sato Y. How can we ameliorate irinotecan-associated diarrhea in children with poor compliance for oral cephalosporin? Pediatr Blood Cancer. 2009;52(1):145.

34. Wagner LM, Crews KR, Stewart CF, Rodriguez-Galindo C, McNall-Knapp RY, Albritton K, et al. Reducing irinotecan-associated diarrhea in children. Pediatr Blood Cancer. 2008;50(2):201-7.

35. Vassal G, Couanet D, Stockdale E, Geoffray A, Geoerger B, Orbach D, et al. Phase II trial of irinotecan in children with relapsed or refractory rhabdomyosarcoma: A joint study of the French Society of Pediatric Oncology and the United Kingdom Children's Cancer Study Group. J Clin Oncol. 2007;25(4):356-61.

36. 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(1):32-7.

37. Vincenzi B, Schiavon G, Pantano F, Santini D, Tonini G. Predictive factors for chemotherapy-related toxic effects in patients with colorectal cancer. Nat Clin Pract Oncol. 2008;5(8):455-65.

38. Iyer L, Hall D, Das S, Mortell MA, Ramírez J, Kim S, et al. Phenotype-genotype correlation of *in vitro* SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. Clin Pharmacol Ther. 1999;65(5):576-82.

39. Ramchandani RP, Wang Y, Booth BP, Ibrahim A, Johnson JR, Rahman A, et al. The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. J Clin Pharmacol. 2007;47(1):78-86.

40. Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008;112(9):1932-40.

41. Stewart CF, Panetta JC, O'Shaughnessy MA, Throm SL, Fraga CH, Owens T, et al. UGT1A1 promoter genotype correlates with SN-38 pharmacokinetics, but not severe toxicity in patients receiving low-dose irinotecan. J Clin Oncol. 2007;25(18):2594-600.

42. McGregor LM, Spunt SL, Furman WL, Stewart CF, Schaiquevich P, Krailo MD, et al. Phase 1 study of oxaliplatin and irinotecan in pediatric patients with refractory solid tumors: A children's oncology group study. Cancer. 2009;115(8):1765-75.

43. Andreyev J, Ross P, Donnellan C, Lennan E, Leonard P, Waters C, et al. Guidance on the management of diarrhea during cancer chemotherapy. Lancet Oncol. 2014;15(10):e447-60.

44. Kehrer DF, Sparreboom A, Verweij J, de Bruijn P, Nierop CA, van de Schraaf J, et al. Modulation of irinotecan-induced diarrhea by cotreatment with neomycin in cancer patients. Clin Cancer Res. 2001;7(5):1136-41.

45. Schmittel A, Jahnke K, Thiel E, Keilholz U. Neomycin as secondary prophylaxis for irinotecan-induced diarrhea. Ann Oncol. 2004;15(8):1296.

46. Alimonti A, Satta F, Pavese I, Burattini E, Zoffoli V, Vecchione A. Prevention of irinotecan plus 5-fluorouracil/leucovorin-induced diarrhea by oral administration of neomycin plus bacitracin in first-line treatment of advanced colorectal cancer. Ann Oncol. 2003;14(5):805-6.

47. de Jong FA, Kehrer DFS, Mathijssen RHJ, Creemers GJ, de Bruijn P, van Schaik RHN, et al. Prophylaxis of irinotecan-induced diarrhea with neomycin and potential role for UGT1A1*28 genotype screening: A double-blind, randomized, placebo-controlled study. Oncologist. 2006;11(8):944-54.

48. Kodawara T, Higashi T, Negoro Y, Kamitani Y, Igarashi T, Watanabe K, et al. The inhibitory effect of ciprofloxacin on the beta-glucuronidase-mediated deconjugation of the irinotecan metabolite SN-38-G. Basic Clin Pharmacol Toxicol. 2016;118(5):333-7.

49. Furman WL, Crews KR, Billups C, Wu J, Gajjar AJ, Daw NC, et al. Cefixime allows greater dose escalation of oral irinotecan: A phase I study in pediatric patients with refractory solid tumors. J Clin Oncol. 2006;24(4):563-70.

50. McGregor LM, Stewart CF, Crews KR, Tagen M, Wozniak A, Wu J, et al. Dose escalation of intravenous irinotecan using oral cefpodoxime: A phase I study in pediatric patients with refractory solid tumors. Pediatr Blood Cancer. 2012;58(3):372-9.

51. Wagner LM, Villablanca JG, Stewart CF, Crews KR, Groshen S, Reynolds CP, et al. Phase I trial of oral irinotecan and temozolomide for children with relapsed high-risk neuroblastoma: A new approach to neuroblastoma therapy consortium study. J Clin Oncol. 2009;27(8):1290-6.

52. DuBois SG, Marachelian A, Fox E, Kudgus RA, Reid JM, Groshen S, et al. Phase I study of the aurora a kinase inhibitor alisertib in combination with irinotecan and temozolomide for patients with relapsed or refractory neuroblastoma: A NANT (New Approaches to Neuroblastoma Therapy) trial. J Clin Oncol. 2016;34(12):1368-75.

53. Goldin BR. Intestinal microflora: metabolism of drugs and carcinogens. Ann Med. 1990;22(1):43-8.

54. Ferencik M, Ebringer L, Mikes Z, Jahnová E, Ciznár I. [Successful modification of human intestinal microflora with oral administration of lactic acid bacteria]. Bratisl Lek Listy. 1999;100(5):238-45.

55. Mego M, Chovanec J, Vochyanova-Andrezalova I, Konkolovsky P, Mikulova M, Reckova M, et al. Prevention of irinotecan induced diarrhea by probiotics: A randomized double blind, placebo-controlled pilot study. Complement Ther Med. 2015;23(3):356-62.

56. Senderovich H, Vierhout MJ. Is there a role for charcoal in palliative diarrhea management? Curr Med Res Opin. 2018;34(7):1253-9.

57. Sergio GC, Felix GM, Luis JV. Activated charcoal to prevent irinotecan-induced diarrhea in children. Pediatr Blood Cancer. 2008;51(1):49-52.

58. Michael M, Brittain MA, Nagai J, Feld R, Hedley D, Oza A, et al. Phase II study of activated charcoal to prevent irinotecan-induced diarrhea. J Clin Oncol. 2004;22(21):4410-7.

59. Hamada A, Aoki A, Terazaki H, Ito K, Yokoo K, Sasaki Y, et al. Pharmacokinetic changes of irinotecan by intestinal alkalinization in an advanced colorectal cancer patient. Ther Drug Monit. 2005;27(4):536-8.

60. Takeda Y, Kobayashi K, Akiyama Y, Soma T, Handa S, Kudoh S, et al. Prevention of irinotecan (CPT-11)-induced diarrhea by oral alkalization combined with control of defecation in cancer patients. Int J Cancer. 2001;92(2):269-75.

61. Takeda Y, Kobayashi K, Akiyama Y, Soma T, Handa S, Kudoh S, et al. [A case-control study of prevention of irinotecan-induced diarrhea: The reducing side effects of irinotecan by oral alkalization combined with control of defecation]. Gan To Kagaku Ryoho. 2002;29(7):1171-7.

62. Sakata Y, Suzuki H, Kamataki T. [Preventive effect of TJ-14, a kampo (Chinese herb) medicine, on diarrhea induced by irinotecan hydrochloride (CPT-11)]. Gan To Kagaku Ryoho. 1994;21(8):1241-4.

63. Trifan OC, Durham WF, Salazar VS, Horton J, Levine BD, Zweifel BS, et al. Cyclooxygenase-2 inhibition with celecoxib enhances antitumor efficacy and reduces diarrhea side effect of CPT-11. Cancer Res. 2002;62(20):5778-84.

64. Horikawa M, Kato Y, Sugiyama Y. Reduced gastrointestinal toxicity following inhibition of the biliary excretion of irinotecan and its metabolites by probenecid in rats. Pharm Res. 2002;19(9):1345-53.

65. Tobin PJ, Beale P, Noney L, Liddell S, Rivory LP, Clarke S. A pilot study on the safety of combining chrysin, a non-absorbable inducer of UGT1A1, and irinotecan (CPT-11) to treat metastatic colorectal cancer. Cancer Chemother Pharmacol. 2006;57(3):309-16.

66. Villalona-Calero M, Schaaf L, Phillips G, Otterson G, Panico K, Duan W, et al. Thalidomide and celecoxib as potential modulators of irinotecan's activity in cancer patients. Cancer Chemother Pharmacol. 2007;59(1):23-33.

67. Govindarajan R, Heaton KM, Broadwater R, Zeitlin A, Lang NP, Hauer-Jensen M. Effect of thalidomide on gastrointestinal toxic effects of irinotecan. Lancet. 2000;356(9229):566-7.

68. Savarese DM, Savy G, Vahdat L, Wischmeyer PE, Corey B. Prevention of chemotherapy and radiation toxicity with glutamine. Cancer Treat Rev. 2003;29(6):501-13.

69. Xue H, Sawyer MB, Field CJ, Dieleman LA, Murray D, Baracos VE. Bolus oral glutamine protects rats against CPT-11-induced diarrhea and differentially activates cytoprotective mechanisms in host intestine but not tumor. J Nutr. 2008;138(4):740-6.

70. Gaurav K, Goel RK, Shukla M, Pandey M. Glutamine: A novel approach to chemotherapy-induced toxicity. Indian J Med Paediatr Oncol. 2012;33(1):13-20.

71. Kee BK, Morris JS, Slack RS, Crocenzi T, Wong L, Esparaz B, et al. A phase II, randomized, double blind trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer treated with irinotecan. Support Care Cancer. 2015;23(3):661-70.

72. Gibson RJ, Stringer AM. Chemotherapy-induced diarrhea. Curr Opin Support Palliat Care. 2009;3(1):31-5.

73. Souid AK, Dubowy RL, Blaney SM, Hershon L, Sullivan J, McLeod WD,

et al. Phase I clinical and pharmacologic study of weekly cisplatin and irinotecan combined with amifostine for refractory solid tumors. Clin Cancer Res. 2003;9(2):703-10.

74. Remington M, Fleming CR, Malagelada JR. Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome. Gut. 1982;23(2):98-101.

75. Nightingale JM, Lennard-Jones JE, Walker ER. A patient with jejunostomy liberated from home intravenous therapy after 14 years; contribution of balance studies. Clin Nutr. 1992;11(2):101-5.

76. Sun JX, Yang N. Role of octreotide in post chemotherapy and/or radiotherapy diarrhea: Prophylaxis or therapy? Asia Pac J Clin Oncol. 2014;10(2):e108-13.

77. Hoff PM, Saragiotto DF, Barrios CH, del Giglio A, Coutinho AK, Andrade AC, et al. Randomized phase III trial exploring the use of long-acting release octreotide in the prevention of chemotherapy-induced diarrhea in patients with colorectal cancer: The LARCID trial. J Clin Oncol. 2014;32(10):1006-11.

78. Al-Hussaini A, Butzner D. Therapeutic applications of octreotide in pediatric patients. Saudi J Gastroenterol. 2012;18(2):87-94.

79. Matheson AJ, Noble S. Racecadotril. Drugs. 2000;59(4):829-35; discussion 836-7.

80. Gordon M, Akobeng A. Racecadotril for acute diarrhea in children: systematic review and meta-analyses. Arch Dis Child. 2016;101(3):234-40.

81. Kang G, Thuppal SV, Srinivasan R, Sarkar R, Subashini B, Venugopal S, et al. Racecadotril in the management of rotavirus and non-rotavirus diarrhea in under-five children: Two randomized, double-blind, placebo-controlled trials. Indian Pediatr. 2016;53(7):595-600.