International Journal of Clinical Medicine, 2014, 5, 393-406
Published Online April 2014 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2014.57054

Anti-Colorectal Cancer Chemotherapy-Induced Diarrhoea: Current Treatments and Side-Effects

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Received 8 January 2014; revised 7 February 2014; accepted 6 March 2014

Abstract

Chemotherapy-induced diarrhoea (CID) is a common side-effect experienced by patients being treated with a variety of antineoplastic agents. Approximately 80% of patients undergoing chemotherapeutic treatment for colorectal and other gastrointestinal cancers present with CID; moreover, about 5% of early deaths associated with combination anti-cancer chemotherapy are due to CID. Chronic post-treatment diarrhoea amongst cancer survivors can persist for more than 10 years greatly effecting long-term quality of life. Gastrointestinal toxicities such as diarrhoea and vomiting are amongst the primary contributors to dose reductions and delays throughout anti-cancer treatment, presenting a significant hurdle in clinical management of anti-cancer regimes and often result in sub-optimum treatment. However, little is known about pathophysiological mechanisms underlying CID. This work provides a review of chemotherapy-induced diarrhoea, current management guidelines, and shortcomings of current treatments as well as emerging and already existing anti-diarrhoeal treatments potentially suitable for CID.

Keywords

Oxaliplatin; Irinotecan, 5-Fluorouracil, Cisplatin, Carboplatin, Chemotherapy, Colorectal Cancer, Chemotherapy-Induced Diarrhoea

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in the western world [1] [2].

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How to cite this paper: McQuade, R.M., *et al.* (2014) Anti-Colorectal Cancer Chemotherapy-Induced Diarrhoea: Current Treatments and Side-Effects. *International Journal of Clinical Medicine*, **5**, 393-406.
http://dx.doi.org/10.4236/ijcm.2014.57054

With global incidence and mortality rates of approximately 1.2 million and 610,000 respectively per year [3], and consequently low 5 and 10 year survival rates, CRC is projected to account for more than 1.6 million deaths annually by 2020 [4], placing it amongst the highest contributors to cancer related deaths globally [3] [5]-[7].

Surgical resection of the tumour-bearing and adjacent segments of intestines is used in an attempt to eliminate all cancer cells. However, about half of patients are diagnosed beyond stage III, where penetration of the intestinal wall and metastasis to surrounding tissues have already occurred; therefore, chemotherapeutic intervention has been implemented as a mainstream adjuvant therapy, broadening the avenues of treatment [7] [8].

Advances in medicine over the last 50 years have widened the prospects of CRC treatment allowing it to be approached and administered in a variety of ways. Surgical resection, radiotherapy and/or chemotherapy depending on the location of tumour may now be combined and tailored for targeted treatment. Furthermore, chemotherapeutics may be manipulated and modified to be delivered as adjuvants, to compliment and/or improve the efficacy of an already delivered drug, as well as being delivered in combination, merging two or more chemotherapeutic agents in a single infusion.

Current combinations of chemotherapeutic agents include 5-fluorouracil (5-FU)/leucovorin with oxaliplatin (FOLFOX), 5-FU/leucovorin and irinotecan (FOLFIRI), capecitabine and oxaliplatin (CAPEOX/XELOX) and 5-FU/leucovorin/oxaliplatin and irinotecan (FOLFOXIRI) [9]-[11]. Several key trials undertaken in 2000 established improved efficacy of FOLFOX and FOLFIRI combinations in metastatic CRC. As a result, FOLFOX and FOLFIRI have become the standard of care throughout most of the world, showing moderate superiority when compared to previous chemo-doublet 5-FU/LV, promoting higher overall survival rates and progression-free survival by approximately 12 months. Although proven to be effective in the treatment of CRC, with mortality rates decreasing by approximately 50% in most parts of the world since 1950 [12]-[14], these cytotoxic chemotherapies are notorious for prompting undesirable neurological and gastrointestinal side-effects (**Table 1**).

Chronic side-effects often result in dose limitations, and in severe circumstances cessation of anti-cancer treatment, presenting a constant challenge in efficient and tolerable treatment of CRC [15]-[21]. Amongst the most common of these dose-limiting side-effects is chemotherapy-induced diarrhoea (CID) affecting approximately 80% of patients undergoing chemotherapeutic treatment for colorectal and other gastrointestinal cancers [20] [22]. Moreover, about 5% of early deaths associated with combination anti-cancer chemotherapy are due to CID [23]. Although there are now established and well-structured guidelines to navigate management of CID, numerous attempts to prevent peripheral and gastrointestinal neurotoxicity have proven ineffective thus far [18] and avenues of treatment are still limited and carry an excessive amount of side-effects including worsening of already chronic gastrointestinal symptoms.

Investigation of the mechanisms underlying adverse effects caused by anti-cancer treatment is imperative for the development of new therapies to target such pathologies as CID, to increase effectiveness of current treatments and improve CRC patients' quality of life.

2. Chemotherapy-Induced Diarrhoea

About 40% of patients receiving standard dose chemotherapy and all patients receiving high dose chemotherapy for gastrointestinal cancers exhibit pain, ulceration, bloating, vomiting and diarrhoea [30] [31]. Recent statistics on colorectal cancer and its treatments indicate that CID occurs at rates as high as 80% in patients [32]. Diarrhoea is a frequently under-recognised clinical hurdle that significantly affects morbidity and mortality of cancer

Table 1. Neurotoxic and gastrointestinal side-effects associated with anti-cancer chemotherapeutic agents used for the treatment of CRC [24]-[29].

Drug	Side-effects
Carboplatin	Cortical blindness, peripheral sensory neuropathy, nausea, vomiting, constipation and ***diarrhoea***.
Cisplatin	Encephalopathy, headache, stroke, seizures, sensory peripheral neuropathy, Lhermitte's sign, muscle cramps, nausea, vomiting and ***diarrhoea***.
Oxaliplatin	Paraesthesia, sensory peripheral neuropathy, nausea, vomiting, weight loss, constipation and ***diarrhoea***.
5-Fluorouracil	Cerebellar dysfunction, inflammatory leukoencephalopathy, peripheral neuropathy, nausea, vomiting, ***severe diarrhoea*** and anorexia.
Irinotecan	Dysarthria, peripheral sensory neuropathy, palmar-plant erythrodysthesia, nausea, vomiting, ***severe diarrhoea***, constipation and anorexia.

patients worldwide [22]. Chemotherapeutic agents most commonly associated with CID include 5-FU, capecitabine, irinotecan and oxaliplatin [32] [33]. Although prevalence and severity of chemotherapy-induced diarrhoea varies greatly based on the combination of chemotherapeutics, certain regimens, especially those containing 5-FU in combination with irinotecan are associated with rates as high as 87% [22] [34] with one third of patients experiencing severe (grade 3 or 4) (**Table 2**) diarrhoea [35].

Though CID is a clearly established side-effect of gastrointestinal cancer treatment, little research is underway to determine its underlying mechanisms. CID is believed to be a form, or by-product, of alimentary mucositis; that is, inflammation and ulceration of the mucous membranes of the digestive tract [37]. Alimentary mucositis occurs as a result of altered intestinal microflora and mucin secretion, and is a highly probable contributor to the development of CID; however the pathophysiology behind CID is extensive and complex and probably results from several overlapping mechanisms [37].

Specific anti-cancer treatments can be directly linked to a variety of different types of diarrhoea including secretory, osmotic, malabsorptive, exudative, motility related and inflammatory; all of which may be differentially diagnosed from varying symptomology [37].

Disruption to water and electrolyte balance within the gastrointestinal tract is a key component in the pathophysiology of all types of diarrhoea. Intestinal water balance involves many complex processes and pathways involving inflammatory mediators, hormones and neuropeptides that are strictly regulated to maintain the integrity of the intestinal wall, efficiency of the circulatory and enteric nervous systems [38] [39].

Prominent intestinal mucosal damage is a theme throughout the literature surrounding CID. Toxicity to the rapidly dividing crypt cells of the intestinal epithelium coupled with destruction and depletion of intestinal enzymes is believed to be a major contributor to the decrease in absorption and increase in fluid secretion seen in CID [30]-[34] [40]. Direct harm to the villi and mature cells of the intestinal wall results in a higher proportion of immature secretory cells, this increase in secretion and decrease in absorptive capacity of the villi alters the osmotic gradient within the gut contributing to the onset of diarrhoea [41]. The osmotic component is believed to be attributable to cytotoxic agent-induced damage to colonic crypts, thereby reducing chloride absorption and causing water to be released into the intestinal lumen [41]. Chemotherapy-induced disturbance to intestinal absorptive capacity causes an increase in solutes within the intestinal lumen; this triggers an osmotic shift of water into the lumen resulting in osmotic diarrhoea [30] [34] [41]. When non-absorbable compounds are retained within the lumen, active transport of water and electrons is initiated to maintain luminal potential as well as to flush foreign matter from the gastrointestinal tract. Coupled with this, inflammation throughout the intestines leads to secretion of factors such as prostaglandins, leukotrienes and cytokines further stimulating secretion and increasing damage to the epithelium and disrupting intestinal water and ion transport resulting in hypersecretion [34] [40]. It is has been suggested that acute diarrhoea experienced 24 - 96 hours post-chemotherapeutic infusion is primarily secretory [32]. However, whether all chemotherapy-induced diarrhoeas are due to changes in epithelial surface area unknown. Damage to the enteric nervous system caused by chemotherapeutic treatments [42] [43] might underlie gastrointestinal secretory and motility disturbances involved in pathophysiology of CID. It is also unclear whether different chemotherapeutic regimens are associated with different types of diarrhoea. Moreover, the pathophysiological mechanisms underlying chronic diarrhoea persisting long after the chemotherapy have not been investigated.

Although the likelihood of CID is typically unpredictable, occurrence of CID has been linked to a variety of patient and treatment-associated risk factors (**Table 3**). It has been found that age >65, gender and low performance status are common patient-associated risk factors as well as associated bowel pathologies and genetic polymorphisms that may affect drug metabolism [34]. Accompanying this, certain chemotherapeutic drugs and administration regimes have been found to increase susceptibility to CID. Most prominently the addition of 5-FU and leucovorin to treatments, and combination of 5-FU with irinotecan and oxaliplatin increase both severity and prevalence of CID [43] [44].

Table 2. Common terminology criteria for diarrhoea [36].

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhoea	Increase of <4 stools per day over baseline.	Increase of 4 - 6 stools per day over baseline.	Increase of >7 stools per day over baseline. Incontinence. Hospitalization.	Life threatening consequences. Urgent intervention indicated.	Death

Table 3. Risk factors for chemotherapy-induced diarrhoea (modified from [34] [45]-[48]).

Patient-associated risk factors	Elderly (>65)
	Female
	Genetic polymorphisms affecting drug metabolism and distribution such as Gilbert's syndrome, Crigler-Najjar syndrome
	Biliary obstruction
	Associated bowel pathology such as inflammatory bowel disease or malabsorption
Treatment-associated risk factors	Irinotecan & 5-FU
	Weekly chemotherapy schedule
	Infusional chemotherapy
	Bolus 5-FU
	Prior history of CID
	Prior or concomitant radiotherapy

3. Impact of CID

Persistent and severe diarrhoea in combination chemotherapy-treated patients often causes malnutrition and dehydration leading to rapid weight loss (cachexia), fatigue, renal failure, haemorrhoids, perianal skin breakdown [49] [50]. In some cases, chemotherapy causes severe intestinal inflammation, bowel wall thickening and ulceration [51]. Thus, CID is a key contributor to the interruptions in optimal clinical outcomes and may lead to life-threatening sequelae [22] [23] [32].

CID is the primary contributor to approximately 60% of treatment alterations, with about 22% of patients receiving dose reductions, 28% of patients having dose delays and complete cessation of treatment in approximately 15% of patients due to severe diarrhoea during the course of treatment [48] [52]. A direct correlation between cumulative dose and severity of CID has been recognised, with high dose regimens associated with higher reported incidence of CID [20] [29]. Early death rates, occurring in approximately 5% of patients undergoing anti-cancer treatment, are primarily due to CID leading to severe dehydration [23].

About 53% of anti-CRC treated patients that receive adjuvant therapies experience grade 3 or 4 CID at some point during the course of treatment and current guidelines recommend aggressive treatment and hospitalization [53]. Thus, CID is fast becoming a major drain on healthcare resources. A recent cost of illness analysis on the economic impact of grade 3 - 4 CID revealed a median hospital stay of 8 days, indicating that CID is a debilitating and costly complication of CRC chemotherapy [48]. The incidence of chronic post-treatment diarrhoea amongst cancer survivors varies from 14% to 49% and episodes of diarrhoea can persist for more than 10 years [54] greatly effecting long-term quality of life.

Long-term psychological effects of treatment-related chronic persistent diarrhoea are rarely recognised. Mental and social health of CID sufferers has been shown to be greatly compromised with known psychological effects of uncontrolled CID including anxiety, depression, social isolation and low self-esteem [55]. More than 30% of CID sufferers experience interference to their daily activities [32].

4. Treatment of CID

Current management of CID is based heavily on the nature and progression of the diarrhoea itself. CID may be classified as complicated or uncomplicated, late or early onset and categorised as persistent or non-persistent depending on the National Cancer Institute's (2009) Common Terminology Criteria for Adverse Effects grading system [32] [36].

Uncomplicated CID can be managed through diet modification and standard dose of recommended drugs such as loperamide, octreotide and tincture of opium in an outpatient setting, however, complicated diarrhoea requires aggressive treatment and hospitalisation where patients are recommended to take anti-diarrhoeal drugs and intravenous fluids [34].

The recommendations of a consensus conference on the management of CID were published in 1998 and updated in 2004 [40] [45]. These publications provide guidelines for evaluation and classification of symptoms of CID (**Figure 1**). Opioid derivatives loperamide and deodorized tincture of opium (DTO), and octreotide are the only drugs recommended in the updated treatment guidelines, due to lack of efficacy and insufficient evidence for benefits of other therapeutic approaches such as prophylactic treatments [22]. Although the National Cancer Institute's Common Terminology Criteria for Adverse Effects grading system has been updated on several occasions, CID management and treatment guidelines have not been changed since 2004. A consensus working statement published in 2007 offered several clinical recommendations and improvement; however no changes to the treatment of CID have been made [35].

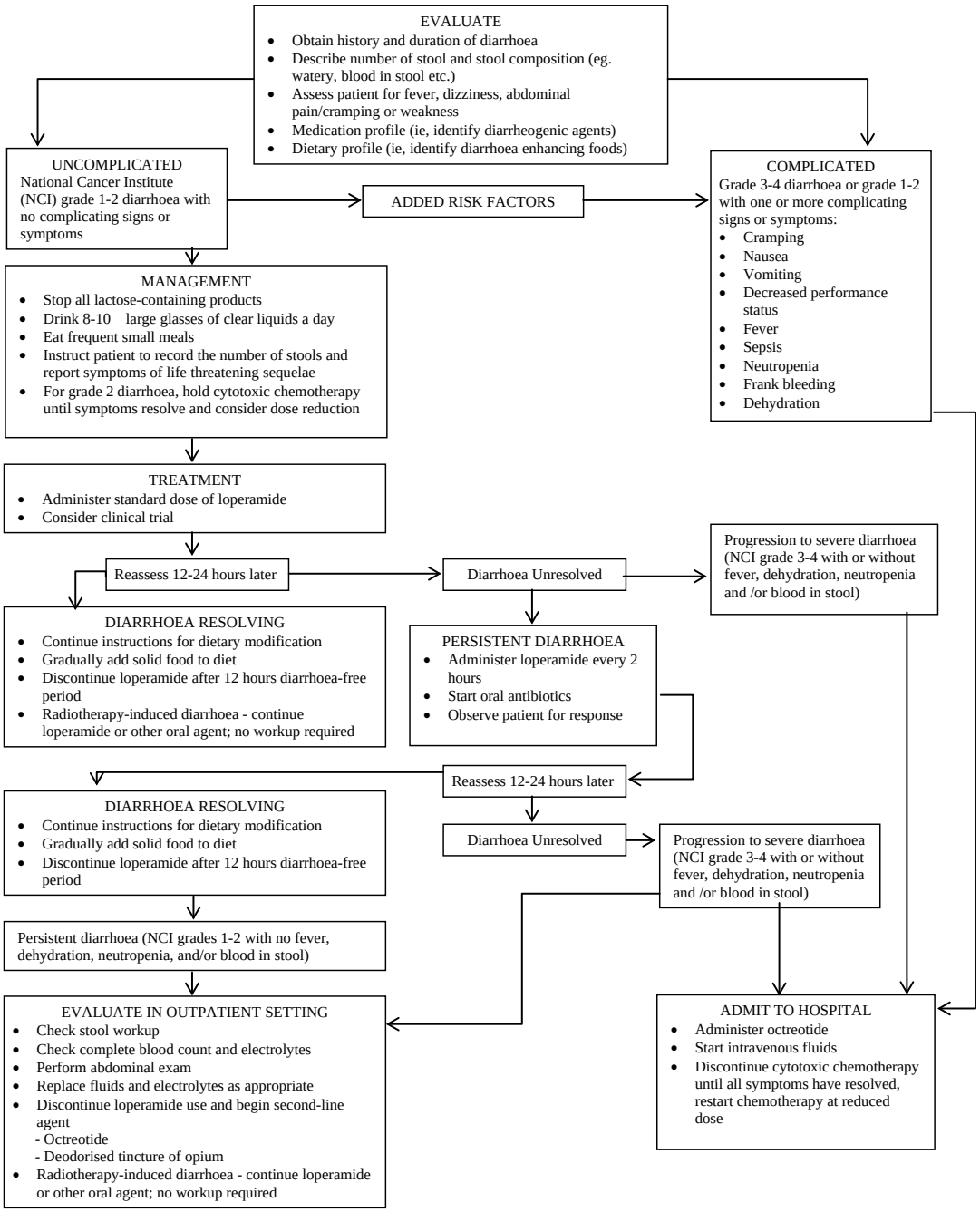

Figure 1. Guidelines for treatment of chemotherapy-induced diarrhoea (modified from [22] [32]).

Until recently the significance of chemotherapy-induced diarrhoea and its impact on regimen designation and treatment efficiency has been greatly underestimated. As a result current treatments available are limited and carry a wide variety of adverse effects including further gastrointestinal symptoms (**Table 4**).

5. National Cancer Institute Guideline-Based Treatment for CID

5.1. Loperamide

Loperamide is a non-analgesic agonist that decreases intestinal motility through an action at μ-opioid receptors of the myenteric plexus [32]. High dose loperamide alleviates diarrhoea associated with chemotherapeutic administration and is the standard first line therapy for CID [22]. However, it is associated with high levels of resistance and failure, specifically when used with irinotecan, and has a variety of side-effects including severe constipation, abdominal pain, dizziness, and rashes and worsening of already present bloating, nausea and vomiting [32] [56]. Clinical studies have also reported incidents of paralytic ileus, in association with abdominal distension occurring in patients administered a very high dose of loperamide [34] [57].

5.2. Octreotide

Loperamide-refractory and complicated diarrhoea are both treated with octreotide [22], an indirect anti-motility substance. Octreotide is a synthetic somatostatin analogue that inhibits specific gut hormones to increase intestinal transit time promoting absorption [38] [49] [58] as well as hyperpolarizing secretomotor neurons within the enteric nervous system to inhibit secretion and promote net absorption [58]. Octreotide has shown to be effective in decreasing CID in clinical trials [38]. However severe adverse effects such as slow and/or uneven heartbeat, severe constipation, severe stomach pain, enlarged thyroid, vomiting, nausea, headache and dizziness occur in more than 10% of patients treated with octreotide [59]. Octreotide is generally reserved as a second line treatment for patients who are unresponsive to loperamide after 48 hours, despite loperamide escalation [32].

5.3. Deodorised Tincture of Opium

Deodorized tincture of opium (DTO) similarly to loperamide, works by activating μ-opioid receptors within the

Table 4. Current treatments and their side-effects for chemotherapy-induced diarrhoea.

Treatment	Mechanism	Side-Effects	References
Loperamide	Synthetic opiate derivative μ-opioid receptor agonist that slows intestinal peristalsis, increases intestinal transit time to promote fluid reabsorption. Also exhibits anti-secretory effects through inhibition of thromboxane-A2.	Stomach pain and bloating, ongoing or worsening of diarrhoea, watery and bloody diarrhoea, severe skin reactions (blistering and peeling), nausea, vomiting, dizziness, drowsiness, severe constipation and paralytic ileus.	[32] [34] [38] [47] [56] [80]
Octreotide	Synthetically engineered somatostatin analogue designed to bind to somatostatin receptors; inhibits adenylyl cyclase to reduce secretion of pancreatic and intestinal hormones, increases intestinal transit time and promotes reabsorption.	Easy bruising and unusual bleeding (nose, mouth, vagina and rectum), purple/red pinpoint spots under skin, slow and/or uneven heart beats, severe constipation, severe stomach pain, enlarged thyroid, vomiting, nausea, headache and dizziness.	[22] [32] [38] [47] [48] [59] [80]
Tincture of opium	Similar to loperamide, acts by activating μ-opioid receptors to slow intestinal peristalsis thereby increasing intestinal transit time and promoting fluid reabsorption.	Vomiting, nausea and light headedness, stomach/abdominal pain, painful/difficult urination, seizures, itching and swelling of the face, tongue and throat, psychological dependence, physical dependence, miosis and respiratory depression.	[22] [34]
Budesonide	Orally administered synthetic steroid with anti-inflammatory effects. Helps to restore mucosal function and improve intestinal fluid reabsorption. Has inhibitory effect on mucosal prostaglandins.	Increased blood pressure, headache, thinning of the skin, easy bruising, muscle pain, stomach pain, indigestion, mild skin rash, changes to menstrual cycle.	[46] [61] [63]
Atropine	Competitive antagonist at muscarinic receptors. Helps to suppress the cholinergic effects of irinotecan.	Allergic reactions (swelling of the lips, tongue and face), irregular or fast heart rate, rash or flushing, eye pain, headache, dizziness, blurred vision, bloating, nausea, heartburn, constipation, weakness, difficulty urinating.	[60]-[62]

gastrointestinal tract to slow intestinal peristalsis, thereby increasing intestinal transit time and promoting fluid reabsorption [34]. Currently there are no studies demonstrating the efficacy of DTO in treatment of CID, but it is still a widely used anti-diarrheal drug and may be considered as a second-line therapy for persistent and uncomplicated diarrhoea [34]. DTO contains 10 mg/ml of morphine, making it one of the most potent forms of orally administered morphine available by prescription. Side-effects of DTO range from euphoria or dysphoria to vomiting, nausea, light headedness, stomach/abdominal pain, painful/difficult urination as well as seizures, itching and swelling of the face, tongue and throat. DTO has also been linked to psychological and physical dependence, meiosis and respiratory depression [22] [34].

6. Prophylactic Measures

6.1. Atropine

Atropine is a competitive antagonist at muscarinic receptors that helps to suppress the cholinergic effects of secretory diarrhoea. Atropine functions by inhibiting the muscarinic actions of acetylcholine released by cholinergic nerve fibres innervating gastrointestinal smooth muscles, as well as inhibiting the actions of cholinergic secretomotor neurons innervating the mucosa. Dosage ranges from 0.25 - 1 mg and can be delivered intravenously or subcutaneously as either prophylaxis or treatment for CID, to a maximum cumulative dose of 1.2 mg [60]. It has been found that subcutaneous administration of atropine prior to chemotherapeutic treatment was effective at reducing CID [60] [61]. However atropine administration is linked to swelling of the lips, tongue and face, irregular or fast heart rate, rash or flushing, eye pain, headache, dizziness, blurred vision, bloating, nausea, heartburn, constipation, weakness, difficulty urinating [60]-[62].

6.2. Budesonide

Budesonide is an orally administered synthetic steroid with anti-inflammatory effects, commonly used in patients with inflammatory bowel disease. It works to restore mucosal function and improve intestinal fluid reabsorption as well as having an inhibitory effect on mucosal prostaglandins. Suppression of inflammation throughout the bowel could potentially contribute to reductions in the occurrence of CID; however published data revealed no significant decreases in incidence of CID from concurrent budesonide and loperamide treatment [63]. Furthermore budesonide has been linked to increased blood pressure, headache, thinning of the skin, easy bruising, muscle pain, stomach pain, indigestion, mild skin rash, and changes to menstrual cycle [46] [61] [63].

6.3. Antibiotics

Several studies have investigated the effectiveness of antibiotic therapy to combat irinotecan-induced diarrhoea [64]. Results surrounding antibiotic use in irinotecan-induced diarrhoea remain controversial. Several studies indicated that elimination of β-glucoronidase producing microflora through the use of antibiotics namely penicillin, streptomycin, cefixime, ceftriaxone, neomycin and levofloxacin may decrease incidence and severity of CID [65]-[67]. In contrary, non-significant reductions in severity and frequency of diarrhoea accompanied by substantially higher rates of grade 2 diarrhoea were found [68]. Moreover, contention over the use of antibiotics in immune compromised patients for risk of *Clostridium difficile* (*C. difficile*) infection causing both nosocomial and antibiotic-associated diarrhoea is evident throughout literature [46] [65] [69]. *C. difficile* is a prominent and potentially life threatening infection that results from disturbance of normal bacterial flora in the colon, triggering release of toxins that cause mucosal inflammation and damage. *C. difficile* infection is most frequent amongst hospitalized patients and it is well known that colorectal cancer, abdominal surgery, as well as a weakened immune system as a result of chemotherapy, increases susceptibility to *C. difficile* infection [70] [71].

6.4. Glutamine

Glutamine is an amino acid found within the gastrointestinal tract, it acts as a major energy source for enterocytes as well as playing an important role in gut integrity and immune responses [72]. It is believed that glutamine can stimulate intestinal mucosa growth, and therefore may reduce gastrointestinal toxicity [32] [73] [74]. Several studies over the last decade have investigated the incidence and severity of CID in patients receiving

prophylactic oral and intravenous glutamine [75]-[79]. It was reported that intravenous administration of 20 g glutamine reduced plasma endotoxin levels and decreased severity of CID [77]. However a more recently conducted meta-analysis concluded that, although glutamine may reduce the duration of CID, it does not reduce its severity [78]. Furthermore, a trial involving high-dose chemotherapy and glutamine-containing intravenous solutions showed significantly higher incidence of relapse and death in patients receiving glutamine [79].

7. Emerging & Potential Treatments for CID

Given that current treatments for CID have limited efficacy and a wide range of adverse effects, the search for and use of alternative anti-diarrhoeal agents with few or no side-effects is essential. Several emerging and already existing treatments for other conditions associated with acute and chronic diarrhoea, such as irritable bowel syndrome (IBS), travellers' diarrhoea and other conditions could be considered and tested for the treatment of CID.

7.1. Adsorbents

Adsorbent substances are emerging as promising avenues in the treatment of CID. Adsorbents work by collecting excess materials on their surface and transporting them through the excretion process. Activated charcoal has long been used in the treatment of acute poisoning and is under investigation as a remedy for the late onset diarrhoea experienced after 5-FU and irinotecan infusions [81]. AST-120 also known as kremazin, a carbon-based adsorbent that is believed to absorb uremic toxins, such as indoxyl sulphate, in the gut has been explored in both cancer patients with irinotecan-induced diarrhoea and nonconstipated IBS sufferers [82] [83]. AST-120 has been found to be safe and well-tolerated, effective in reducing pain and bloating in nonconstipated IBS sufferers and to ameliorate irinotecan-induced diarrhoea without disrupting clearance of irinotecan metabolites.

7.2. Chloride Channel Inhibitors

Chloride is an essential ion in intestinal secretion and absorption. Secretory diarrhoea, such as that experienced in irinotecan-treated patients, results from a combination of excessive secretion and reduced absorption in the intestinal lumen [84] [85]. Excessive fluid secretion is driven by active chloride secretion, followed by secondary movement of water and sodium into the intestine. Deliberate inhibition of calcium-activated chloride channels located on enterocytes throughout the intestines reduces excretion of chloride into the intestinal lumen and consequently decreases the presence of water and sodium, diminishing the symptoms of diarrhoea [86].

7.3. Kappa Opioid Receptor Agonists

Opioid receptors (μ (mu), δ (delta) and κ (kappa)) located throughout the peripheral and central nervous systems participate in inhibition of perception of noxious stimuli from the gastrointestinal tract [87]. Although effective as anti-diarrhoeal agents both μ and δ agonists have many adverse effects such as constipation and opioid dependence, which impede their general use in clinical practice [87]. However, κ-opioid receptor agonists seem to be devoid of these symptoms.

Asimadoline is a highly selective and potent κ-opioid receptor agonist that is predominantly peripherally restricted at doses below 5 mg [88]. In clinical trials conducted in IBS patients it displayed a significant improvement in frequency/urgency of stools and pain free days and adequate relief of pain scores [89] [90]. Although there was no significant improvement in primary end point (number of months accrued with adequate relief of pain), asimadoline appeared to be well tolerated and produced overall improvement of gastrointestinal symptoms, including diarrhoea [90] highlighting that it could be used as a potential therapeutic for CID given that pain relief is not a primary concern in CID sufferers.

7.4. Enkephalinase Inhibitors

Enkephalins are endogenous neurotransmitters found throughout the enteric nervous system. Known to be pro-absorptive and anti-secretory in nature, enkephalins act on δ-opioid receptors, increasing chloride absorption and inhibiting adenylate cyclase to reduce intestinal secretion. Endogenous enkephalins are rapidly degraded by

enkephalinase. Inhibition of enkephalinase has recently been tested for anti-secretory effects against numerous secretagogues including cholera toxin and prostaglandins. Racecadotril is a powerful enkephalinase inhibitor with its active metabolite thiorphan being effective in clinical management of acute diarrhoea in both adults and children [91] [92]. Clinical trials of racecadotril have primarily been undertaken in patients with acute diarrhoea of presumed infectious origin and chronic HIV-related diarrhoea. Racecadotril significantly decreases mean stool output and duration of acute diarrhoea in both adults and infants when compared to placebo [93] [94], and has a similar efficacy to loperamide [91] [95] [96], but appears to be better tolerated than loperamide in both adults and children [97].

7.5. Cannabinoids

The effects of cannabinoids are primarily mediated by cannabinoid receptors, a widely expressed class of G-protein coupled receptors. Currently known two receptor subtypes, CB_1 and CB_2, are the main constituent of the endocannabinoid system. Recent studies have found that endocannabinoids acting on myenteric cannabinoid receptors can inhibit colonic propulsion [98] [99]. Dronabinol, a non-selective cannabinoid receptor agonist inhibits colonic motility in healthy subjects [98] [99] and patients with IBS-related diarrhoea [100].

8. Conclusion

Combination therapies now represent the standard first-line of treatment in CRC worldwide, with statistics showing great potential to increase overall survival in locally resected stage III CRC. Chemotherapy-induced gastrointestinal toxicity persists as a major contributor to dose delays, reductions and treatment terminations. Chemotherapy-induced diarrhoea is one of the most common disruptions in clinical management of CRC, affecting a vast majority of patients being treated with combination or adjuvant therapies containing 5-FU and irinotecan. Current treatments for CID are limited and have an abundance of concomitant symptoms; but novel and emerging anti-diarrhoeal treatments may present an additional unexplored avenue of treatments for CID sufferers. Ongoing investigation to identify potential targets and innovative treatment agendas to decrease chemotherapy-related toxicity is essential to improve clinical outcomes and quality of life amongst CID sufferers.

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Abbreviations

5-FU: 5-Fluorouracil
CAPEOX: Combination of Capecitabine and Oxaliplatin. Also known as XELOX.
CID: Chemotherapy-Induced Diarrhoea
CRC: Colorectal Cancer
DTO: Deodorized Tincture of Opium
FOLFIRI: Combination of 5-Fluorouracil, Irinotecan and Leucovorin.
FOLFOX: Combination of 5-Fluorouracil, Oxaliplatin and Leucovorin.
FOLFOXIRI: Combination of 5-Fluorouracil, Oxaliplatin, Irinotecan and Leucovorin
HIV: Human Immunodeficiency Virus
IBS: Irritable Bowel Syndrome
NCI: National Cancer Institute
XELOX: Combination of Capecitabine and Oxaliplatin. Also known as CAPEOX.