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Pharmacological Strategies To Reduce Chemotherapy-Induced Gastrointestinal Toxicity

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Abstract
Chemotherapy induced gastrointestinal dysfunction is a common occurrence associated with many different classes of chemotherapeutic agents. Gastrointestinal toxicity includes mucositis, diarrhea, and constipation, and can often be a dose-limiting complication, induce cessation of treatment and could be life threatening. Modulating the gut microbiome to alleviate chemotherapy-induced gastrointestinal toxicities by combining antibiotics with patient-specific probiotics/fecal microbiota transplants to target pathogenic bacteria and replenish the commensal microbiome remains an exciting prospect.
In this review, we discuss our current understanding of the mechanisms underlying chemotherapy-induced diarrhea and mucositis, and emerging mechanisms involving the enteric nervous system, smooth muscle cells and enteric immune cells.
In fact, 60%–100% of patients on high-dose chemotherapy suffer from gastrointestinal side effects. Therefore, there is a great unmet therapeutic need for preventing and treating chemotherapy-induced gastrointestinal toxicities in the clinic. Recent evidence has also implicated gut dysbiosis in the pathogenesis of not only chemotherapy-induced mucositis and diarrhea, but also chemotherapy-induced peripheral neuropathy. Oxidative stress induced by chemotherapeutic agents results in post-translational modification of ion channels altering neuronal excitability. Thus, investigating how chemotherapy-induced changes in the gut- microbiome axis may lead to gut-related toxicities will be critical in the discovery of new drug targets for mitigating adverse gastrointestinal effects associated with chemotherapy treatment.
Keywords: *Chemotherapy, gastrointestinal, toxicity, diarrhea, mucositis, perpetual neuropathy, treatment, therapy, antibiotics, Chemotherapeutics.*

Purpose
The overall aims of any intervention are to reduce the GI related symptoms experienced by cancer patients—this would relieve suffering, enable dose escalation, or avoid dose de-escalation. Interventions can include prophylactic treatments such as probiotics and antibiotics to prepare the GI tract. They may also include anti-oxidants, anti-inflammatory drugs, and apoptosis inhibitors during cytostatic treatment to alleviate some of the immediate toxicities and associated effects.

Introduction
Current chemotherapeutic regimens do not differentiate between cancer cells and normal cells such as those lining the epithelium of the gastrointestinal tract. This non-specific targeting of rapidly dividing cells results in many gastrointestinal related side effects. Chemotherapy-induced gastrointestinal (GI) toxicities are prevalent among a wide array of chemotherapeutic and radiation regimens. It is estimated that 40% of patients receiving standard dose chemotherapy will develop GI-related toxicities, while significantly greater incidence rates have been reported in patients receiving higher drug doses. In fact, it is estimated that approximately 60%–100% of patients on high dose chemotherapy will experience GI toxicities [5,6,7]. Clinical symptoms typically manifest as nausea, constipation, vomiting, diarrhea, abdominal pain, weight loss and ulcerations within the mucosa. [5,6]. The prevalence and severity of these GI toxicities is dependent on the type of chemotherapy and the dose regimen.
A large number of chemotherapeutic agents used for the treatment of different cancers affect the epithelial barrier integrity. The gut epithelium contains rapidly dividing cells and therefore presents a significant target for the chemotherapeutic agents acting either directly or indirectly to initiate the disruption of the epithelial

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barrier. The current understanding of underlying mechanisms that contribute to these toxicities involve enterocytes, smooth muscle, enteric neurons, and immune cells [5,6,7].

Chemotherapy induced diarrhea (CID)

Diarrhea is a common side effect of chemotherapy, especially in patients suffering from advanced cancers. It is estimated that about 50%–80% of cancer patients suffer from chemotherapy-induced diarrhea (CID) [1,3]. CID is associated with a failure to retain fluid and electrolytes resulting in severe dehydration and electrolyte imbalances, malnutrition, or renal and cardiac dysfunction, all of which can lead to hospitalization and in severe cases, death.

Treatment of CID

Treatment of chemotherapy-induced diarrhea is based on the severity of the diarrhea. The first line defense in treatment of CID is loperamide. Loperamide is a peripherally restricted mu opioid receptor agonist that decreases secretion and reduces intestinal motility by inhibition of enteric neurons. Patients receive escalating doses of loperamide to control symptoms. High dose loperamide remains the primary treatment for the acute management of CID (grades 1–2) with the clinical guidance of a maximum daily dosing of up to 24mg in man [2].

The second line treatment in CID is often octreotide, a synthetic somatostatin analogue which decreases secretion and promotes absorption. Octreotide is generally recommended for patients which refractory to loperamide [3,4]. The mechanism of action involves inhibition of serotonin, vasoactive intestinal peptide and gastrin and enhances intestinal motility [5].

Chemotherapy-induced mucositis (CIM)

Damage to the gastrointestinal mucosa is a common consequence of both radiation therapy and chemotherapy. Chemotherapy-induced mucositis (CIM) is a major dose limiting side effect that can affect many parts of the gastrointestinal tract, although predominantly in the small intestine, oral and oropharyngeal mucosal linings [5,6].

Treatment of CIM

The gastrointestinal tract mucosa and submucosa rely on rapidly dividing stem cells within the crypts for renewal and normal physiological function, and therefore preventing apoptosis induced by chemotherapeutics is another well-established pre-clinical strategy to manage the development of mucositis. For example, CXCL9 mitigated 5-FU-induced intestinal mucositis and mucosal damage by protecting stem/progenitor cells against unregulated cell death induced by chemotherapy [14].

Inflammatory cytokine—G-coupled estrogen receptor (GPER), which is expressed in intestinal crypts, has been reported to exhibit protective effects on intestinal architecture during colitis and ischemia by inhibiting inflammation-driven apoptosis of crypt cells, particularly during colitis and ischemia [7,14].

Vitamin D has been widely shown to have a host of anti-inflammatory and immunomodulatory effects in the intestine, as well as anticancer properties and therefore, may reduce severity of gastrointestinal mucositis. Lastly, treatments such as incretins and growth hormones can be used after cytostatic dosing to benefit the mucosal adaptation and proliferation processes after injury [14].

The gut and chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and often dose-limiting complication of cancer therapy utilizing taxanes (docetaxel or paclitaxel), platinum compounds (cisplatin, carboplatin, and oxaliplatin) as well as other drugs such as vincristine, and bortezomib. Clinical manifestation of symptoms can vary greatly between patients, but often includes all or some of the following: thermal and mechanical hyperalgesia, tactile and thermal allodynia, spontaneous pain [8].

Chemotherapy-induced nausea and vomiting (CINV) is another common GI side effect that can cause significant distress in cancer patients [9,10]. There are currently a number of effective prophylactic strategies for CINV. Options include 5-HT3 receptor antagonists (such as ondansetron), NK-1 receptor antagonists (such as aprepitant), glucocorticoids (such as dexamethasone), and olanzapine, a second-generation antipsychotic [11,12].

Communicating With Patients

As physicians, we are always balancing the benefits and risks of a particular treatment. There must be a shared decision-making process from start to finish from deciding which chemotherapy to use to changes in dose to

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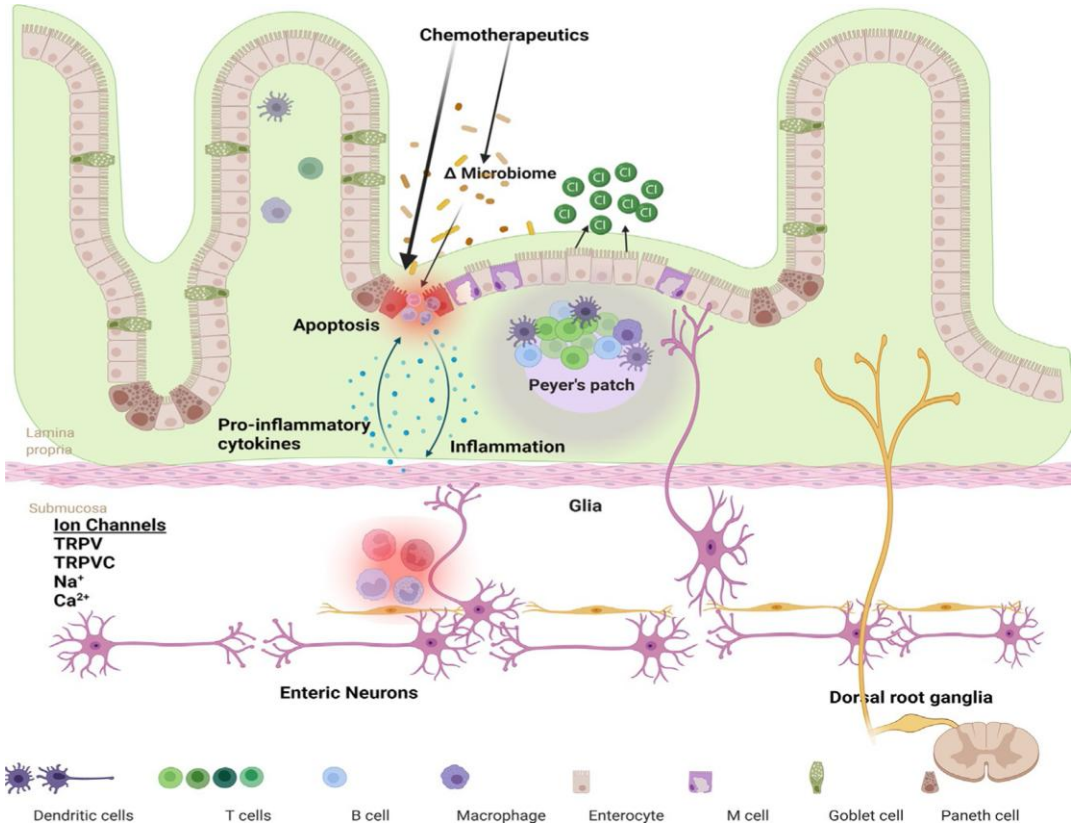
pausing treatment. As our patients are going through the hardest times of their lives while in treatment, it is our duty and privilege to listen, educate and care for them during that process.

Managing Chemotherapy Toxicities:

Significant unmet needs remain in a few areas, including chemotherapy-induced neutropenia, patients with chronic nausea or diarrhea after chemotherapy and chemotherapy-induced peripheral neuropathy. Better management of these residual unmet needs will improve patient quality of life during and after treatment, reduce risk associated with serious complications and ultimately improve chemotherapy outcomes.

Mechanism of Action of Chemotherapeutics



Materials and methods

This review was conducted through a comprehensive analysis of preclinical and clinical studies focused on chemotherapy-induced gastrointestinal toxicities (CIGT), such as diarrhea, mucositis, and peripheral neuropathy. A systematic literature search was performed using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar, covering publications from 2000 to 2025.

The inclusion criteria for the review encompassed studies involving adult cancer patients undergoing chemotherapy, research exploring the mechanisms of GI toxicity, and studies reporting therapeutic or prophylactic strategies including pharmacological agents (loperamide, octreotide, corticosteroids), immunomodulators (GPER agonists, vitamin D), and microbiota-targeted therapies (probiotics, fecal microbiota transplantation). Studies focusing solely on radiation-induced toxicity, pediatric populations, or lacking mechanistic insight were excluded.

The data extracted were categorized based on the type of GI toxicity (diarrhea, mucositis, nausea/vomiting), implicated chemotherapeutic agents, mechanisms of injury (epithelial barrier damage, oxidative stress, enteric nervous system involvement), and therapeutic interventions. Particular attention was given to the role of the gut-brain axis and gut microbiota dysbiosis in mediating or exacerbating toxicity symptoms.

The pathophysiological insights related to enterocyte apoptosis, inflammation, smooth muscle dysregulation, and altered neuronal excitability were synthesized from multiple sources to provide a comprehensive understanding of chemotherapy-induced complications.

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Additionally, evidence-based treatment approaches were reviewed, including the use of loperamide as first-line therapy for chemotherapy-induced diarrhea (CID), and octreotide as second-line management. The role of vitamin D, incretins, and growth factors in ameliorating mucositis was also explored. Recent experimental data supporting the use of G-protein coupled estrogen receptor (GPER) modulators and CXCL9 for protecting intestinal crypt cells were included to highlight emerging molecular targets.

No human or animal subjects were directly involved in this review; therefore, ethical approval and informed consent were not required. The findings of this study aim to contribute to the development of targeted strategies for reducing gastrointestinal side effects in cancer patients undergoing chemotherapy.

Results

This article is based on an extensive review of peer-reviewed clinical studies, meta-analyses, and systematic reviews. A schematic presentation of mechanisms that underlie the chemotherapy-induced gastrointestinal toxicity. Chemotherapeutics can alter gut microbiome directly or through effects on the epithelial cells. Disruption of the gut barrier results in bacterial translocation and an inflammatory response within the lamina propria. This can affect ion channels in enteric and extrinsic sensory neurons projecting from the dorsal root ganglia. Inflammation also induces increase in epithelial secretions resulting in diarrhea. Injury to DNA of intestinal epithelial cells induce apoptosis.

Effective prophylaxis and treatment of CINV are crucial for patient comfort and adherence to chemotherapy regimens. The European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC) recommend a combination of antiemetic agents based on the emetogenic potential of the chemotherapy - 5-HT3 receptor antagonists, corticosteroids.

These recommendations align with those from the American Society of Clinical Oncology (ASCO), emphasising a tailored approach based on individual patient risk factors and chemotherapy regimen.

It's important to note that while these strategies are supported by clinical evidence, their implementation should be individualised based on patient-specific factors and in consultation with oncology specialists.

Conclusion

Chemotherapy-induced gastrointestinal toxicities, including diarrhea and mucositis, are major hurdles in cancer treatment. Despite major advances in chemotherapy, treatment of gastrointestinal toxicity remains inadequate often resulting in hospitalisation, cessation of treatment and decrease in quality of life. In this review, we highlighted our current understanding of the pathophysiology (Fig. 1) and potential pharmacological approaches to treat CID and CIM.Future studies to dissect individual cell type specific responses in the gastrointestinal tract to chemotherapeutic agents will provide significant insights for treatment of gastrointestinal toxicities.

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