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Systemic treatment-induced gastrointestinal toxicity: incidence, clinical presentation and management

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Abstract

The toxicity of cancer chemotherapy is among the most important factors limiting its use. Clear delineation and communication of benefits and risks is an essential component of treatment decisions. Gastrointestinal toxicity during chemotherapy is frequent and contributes to dose reductions, delays and cessation of cancer treatment. The development of intervention strategies that could eliminate an expected side effect of chemotherapy is vital. Physiologic changes that can increase the toxicity of chemotherapy are decreased stem cell reserves, decreased ability to repair cell damage, progressive loss of body protein, and accumulation of body fat. Symptoms only arise when physiological functions are altered. The gastrointestinal symptoms arising during cancer chemotherapy can often be cured if newly acquired, and if gastrointestinal physiological deficits are identified. Developing new chemotherapy regimens with similar efficacy but less toxicity should be a priority for future research.

Keywords chemotherapy, gastrointestinal toxicity, cancer

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Introduction

Gastrointestinal toxicity is a common complication of cytotoxic cancer chemotherapy. Currently available cytotoxic drugs do not discriminate between cancer cells and normal cells undergoing rapid division. The toxicity of anticancer treatment will continue to be a significant problem until therapies highly selective for malignant cells are developed [1]. Combination regimens are often the standard treatment. The rapid extension of available anti-neoplastic drugs has, however, also emphasized the urgent need for clinicians to better understand and detect the spectrum of acute and late toxicities of these regimens.

We reviewed the English-language medical literature published from January 1966 to September 2011 and identified more than 350,000 publications related to cancer and its therapies [2]. Our effort was to study relevant publications based on a narrative literature review and highlight the incidence, pathophysiology and therapeutic management of chemotherapy-induced gastrointestinal toxicity.

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Tubulin poisons

Taxanes are mitotic inhibitors and work by disrupting polymerization. The principal mechanism through which the taxanes stabilize microtubules is the strengthening of the lateral interactions between protofilaments [3]. It is difficult to compare docetaxel and paclitaxel in terms of gastrointestinal toxicity; however docetaxel seems to be associated with more side effects than paclitaxel. Taxane-based chemotherapy regimens have been associated with a wide spectrum of colitis (Table 1). The most frequent type of colitis is the ischemic. Severe complications including bowel necrosis, colonic perforation or typhlitis have been described. Ischemic colitis presents with a symptom complex of acute abdominal pain and direct or rebound tenderness and possibly associated neutropenia, fever and/or diarrhea, with or without blood. Septicemia frequently occurs and the most common causative organism is aerobic gram-negative bacteria. Colonoscopy is associated with an increased risk of perforation and, therefore, it should be discouraged. The histopathological analysis is compatible with a significant component of inflammatory changes, including mucosal and submucosal edema, hemorrhage, acute inflammatory infiltrates, mucosal ulceration and serositis (Fig. 1, 2) [4]. Early detection allows the majority of cases to be resolved with non-operative management and supportive care, such

Table 1 Drug, gastrointestinal, gastrointestinal toxicity, incidence, and histology

Drug	Gastrointestinal toxicity	Prevalence	Histology
Taxanes	Nausea	40%	Ischemic colitis, neutropenic colitis, ischemia with venous thromboses within the wall of the bowel
	Diarrhea	37-40%	
	Vomiting	25%	
	Stomatitis	42-47%	
	SGOT, SGPT greater than 1.5 times the upper limit of normal	18%	
	Bilirubin in the upper limit of normal	9%	
	ALP greater than 2.5 times the upper limit of normal	7.5%	
	SGOT or/and SGPT greater than 1.5 times the upper limit of normal concomitant with ALP greater than 2.5 times the upper limit of normal	4.5%	
	Hepatitis	rare	
	Colitis	1.9%	
Platinum compounds (cisplatin, carboplatin)	Vomiting < 60 mg/m^2	60-90%	
	Vomiting > 60 mg/m^2	> 90%	
	Hepatic toxicity - SGOT	Rare, minor elevations	
	Diarrhea		
	Elevated serum amylase		
	Hiccups		
Oxaliplatin	Nausea	74%	Perisinusoidal fibrosis, hepatocytes show atrophic changes
	Diarrhea	56%	
	Vomiting	47%	
	Stomatitis	42%	
	Anorexia	29%	
	Abdominal pain	33%	
	Gastroesophageal reflux	5%	
	Constipation	32%	
	Dyspepsia	14%	
	Transaminases elevation	57%	
	ALP elevation	42%	
	Bilirubinemia	20%	
Anthracyclines	Stomatitis	> 80%	Focal infiltration by inflammatory cells and steatosis
	Ulceration of esophagus and the colon		
	Anorexia	15%	
	Diarrhea	15%	
	Tongue hyperpigmentation	Rare	
	Nausea and vomiting	20-85%	
Fluoropyrimidines	Stomatitis	23%	Severe acute hepatitis involving the lobules and portal zones with evidence of cholangitis and bile duct proliferation, portal and mild lobular fibrosis, iron deposition both within the hepatocytes and the Kupffer cells
	Esophagopharyngitis		
	Diarrhea	50%	
	Anorexia		
	Nausea	44%	
	Vomiting	26%	
	Proctitis		
	Mucositis		
	Hyperbilirubinemia	34%	
Cytarabine, Gemcitabine	Oral and anal inflammation or ulceration	frequently	Necrotizing colitis, veno-occlusive disease
	Anorexia	frequently	
	Nausea	frequently	
	Vomiting	frequently	
	Diarrhea	frequently	
	Bowel necrosis		
	Stomatitis		
	Pancreatitis		
	Hepatic dysfunction		

Drug	Gastrointestinal toxicity	Prevalence	Histology
Methotrexate	Nausea	10-80%	
	Vomiting	10-80%	Macrosteatosis, fibrosis, fatty change, focal hepatitis, cirrhosis, low grade portal inflammation, hepatocellular carcinoma (case reports)
	Diarrhea	10-80%	
	Stomatitis	10-80%	
	Pharyngitis		
	Anorexia		
	Melena		
	Gastrointestinal ulceration		
	Enteritis		
	Elevations of aminotransferases and serum lactate dehydrogenase	14.1%	
	Acute hepatitis		
	Chronic fibrosis		
	Cirrhosis		
	Decrease in serum albumin		
Alkylators	Nausea and vomiting	70-90%	Massive hepatic necrosis, necrosis of perivenous hepatocytes and diffuse hepatocellular damage with mild steatosis
	Anorexia	Less frequently	
	Abdominal discomfort, pain	Less frequently	
	Diarrhea	Less frequently	
	Hemorrhagic colitis	Less frequently	
	Elevated hepatic enzymes	Few reports	
Ifosfamide	Nausea and vomiting	60-80%	Cytolytic or cholestatic features or evidence of vascular injury
	Anorexia	infrequently	
	Diarrhea	infrequently	
	Constipation	infrequently	
	Stomatitis	infrequently	
	Mucositis	infrequently	
	Pancreatitis	Rare	
	Elevated hepatic transaminases	1-3%	
Nitrosoureas	Nausea and vomiting		
	Anorexia		
	Stomatitis	Infrequently	
	Mucositis	rare	
	Increased transaminases, ALP an bilirubin levels	In a small percentage of patients	
Dacarbazine-Procarbazine	Nausea and vomiting	35%	Granulomatous hepatitis with tissue eosinophilia
	Stomatitis		
	Melena		
	Diarrhea		
	Anorexia		
	Abdominal pain		
	Constipation		
	Dry mouth		
	Granulomatous hepatitis		
	Hepatic dysfunction, Hepatic vein thrombosis		

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ALP, alkaline phosphatase

as administering anti-peristaltic agents, aggressive fluid resuscitation, bowel rest and broad antibiotic coverage. Surgical intervention is mandatory for peritonitis, bowel perforation, or gastrointestinal hemorrhage that persists despite correction of coagulopathy, and consists usually of bowel resection and stoma creation (Table 3). Some authors argue that dose adjustments or discontinuation of the culprit agent may successfully prevent recurrences of colitis [4].

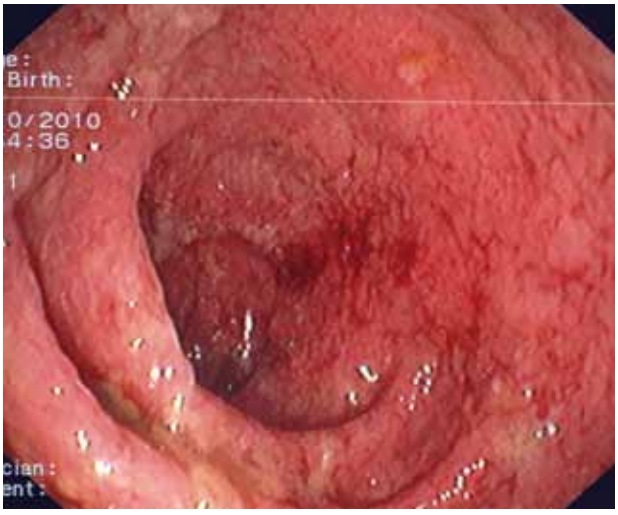

Figure 1 Endoscopic picture of a patient who received docetaxel and developed ischemic colitis. Bowel mucosa shows friability, diffuse profound ulcers and spontaneous bleeding

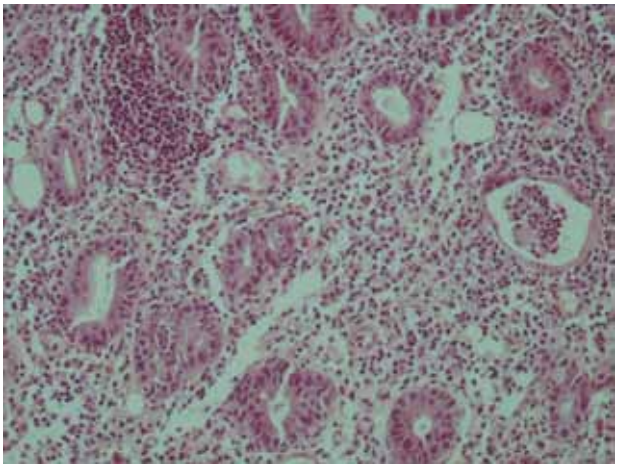

Figure 2 Colonic biopsy of the above patient: Prominent inflammation of the lamina propria and cystic dilation of the crypts with increased apoptosis and conspicuous crypt abscesses (H & E * 200)

Platinum adducts

Cisplatin is a square planar molecule, which has two chloride and two ammonia ligands in the cis-configuration. Once in the cell, platinum complexes are able to react with nucleophiles, such as DNA bases, RNA and proteins, to form adducts. The actual pathway from DNA damage to cell death involves many steps, resulting finally in apoptosis or programmed cell death [5]. Cisplatin is highly protein bound, and renally excreted, which result in nephrotoxicity [6]. Cisplatin in doses of 50-120 mg/m^2 will cause emesis in the majority of patients within 24 h of administration. A peak in urinary metabolites of serotonin occurs 6 h after cisplatin administration suggesting a strong correlation of serotonin release and vomiting with this agent. Delayed emesis occurs 24 h or more after chemotherapy has been administered. Cisplatin causes the most severe delayed emesis [7]. Diarrhea, hiccups, and elevated serum amylase have also been described (Table 1). Carboplatin is a cisplatin analogue that is less potent but more stable, with a longer half life. However, toxicity profiles are different, with carboplatin being much less nephrotoxic and neurotoxic, but causing more bone-marrow suppression. Vomiting occurs in 65% of the patients and in about one-third of these patients it is severe (Table 1). Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin. Other gastrointestinal effects observed frequently were pain, in 17% of the patients, diarrhea in 6% and constipation also in 6% [8].

Oxaliplatin is a third-generation platinum analogue. It has at least equivalent potency when compared with cisplatin but, more interestingly, a degree of non-cross resistance with other platinum compounds. Gastrointestinal side effects include basically diarrhea and nausea, often vomiting, stomatitis, abdominal pain and anorexia and rarely gastroesophageal reflux (Table 1). Additional side effects possibly related to treatment in 2-5% of patients include dry mouth, melena, gingivitis, rectal hemorrhage, hemorrhoids, hemoptysis, proctitis, tenesmus. Ileus, pancreatitis, hepatic sinusoidal dilatation and colitis (including *Clostridium difficile* diarrhea) have also been reported [9].

DNA intercalators

Numerous mechanisms have been proposed to be responsible for intercalator-mediated cytotoxicity, including inhibition of DNA topoisomerase II and DNA replication. Emerging evidence indicates that chemotherapeutic drugs can alter DNA methylation patterns [10]. Gastrointestinal side effects include acute nausea and vomiting in 20-85% of patients. Stomatitis has been reported in up to 80% of patients and is dose and schedule related. Ulceration of the esophagus and the colon has also been described. Approximately 15% of patients present with anorexia and diarrhea. Rare cases of tongue hyperpigmentation have also been associated with the use of doxorubicin. Stomatitis or other ulcerations typically occur 2 to 10 days after administration and, if severe, can be complicated by bleeding or local infection (Table 1). Severe cases of colonic ulceration can be fatal. Nausea and vomiting are preventable with appropriate antiemetic therapy [11].

Antimetabolites

Antimetabolites were among the first effective chemotherapeutics discovered and are folic acid, pyrimidine or purine analogues. They have similar structures to naturally occurring molecules used in nucleic acid (DNA and RNA) synthesis. Generally, antimetabolites induce cell death during the S phase of cell growth when incorporated into RNA and DNA or inhibit enzymes needed for nucleic acid production [12].

5-Fluorouracil (5-FU) is an analogue of uracil that is converted by multiple alternative biochemical pathways to several cytotoxic forms [13,14]. Gastrointestinal side effects can be severe and life-threatening with 5-FU. Stomatitis and esophagopharyngitis, diarrhea, anorexia, nausea and emesis are commonly seen during therapy. The mucositis and diarrhea are dose limiting. Mucositis may be preceded by a sensation of dryness, followed by erythema and formation of white, patchy membrane, ulceration, and necrosis. The diarrhea may be bloody (Table 1). Profuse nausea, vomiting and diarrhea can lead to dehydration and hypotension [15]. Octreotide has been shown to be more effective than loperamide for the treatment of 5-FU-induced diarrhea (Table 3). An oral hygiene program is often instituted for reducing the severity of mucositis, and topical anesthetics can provide local pain relief. Allopurinol mouthwashes have shown little benefit in the amelioration of 5-FU-induced mucositis. Oral cryotherapy with ice chips or popsicles for 30 min prior to bolus infusions of 5-FU has been shown to decrease the acuteness of mucositis. 5-FU has not been reported to cause liver damage when given orally and only rare reports of possible hepatotoxicity have been noted.

Capecitabine is an orally available tumor-selective fluoropyrimidine carbamate [16]. Gastrointestinal side effects include mainly diarrhea, nausea, vomiting, stomatitis, abdominal pain and infrequently constipation and dyspepsia. Hepatic side effects consist of hyperbilirubinemia and hepatic failure [17].

6-Mercaptopurine (6-MP) is an analogue of the natural purine base hypoxanthine. It is active in the S phase of cell proliferation. It is absorbed well orally and dissected by hepatic xanthine oxidase to inactive metabolites. Allopurinol can inhibit this enzyme and therefore if both drugs are co-administered, care is needed in order to reduce the risk of increased toxicity [18]. Gastrointestinal effects include intestinal ulceration. Nausea, vomiting, and anorexia have been infrequently reported during initial administration. Mild diarrhea and sprue-like symptoms are occasionally experienced. An increased risk of pancreatitis may be associated with the investigational use of mercaptopurine in inflammatory bowel disease. Oral lesions resemble thrush rather than antifolic ulcerations [19].

Cytarabine follows the same metabolic pathways and thus requires to be transported to the cell for activation. Cytarabine triphosphate (ara-CTP) is the cytotoxic metabolite of cytarabine and is considered as an S-phase-specific drug, although it is active at other phases of the cycle [20]. Gastrointestinal side effects comprise oral and anal inflammation or ulceration, anorexia, nausea, vomiting, and diarrhea. Nausea and vomiting most frequently follows rapid intravenous injection. Bowel necrosis, stomatitis, pancreatitis and hepatic dysfunction have also been described (Table 1) [21] .

Gemcitabine is a pyrimidine analogue structurally similar to cytarabine. Accumulation of its active cytotoxic metabolite is higher than ara-CTP and its elimination is much more prolonged. Gemcitabine can be incorporated both into DNA and RNA [22]. In the aspect of the gastrointestinal toxicity, nausea and vomiting were commonly reported but were usually of mild to moderate severity. Diarrhea and stomatitis occur less frequently. Gemcitabine was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to gemcitabine (Table 1) [23] .

Methotrexate primarily inhibits dihydrofolate reductase (DHFR), an enzyme that functions to catalyze the conversion of dihydrofolate to tetrahydrofolate, which, in turn, is converted to a variety of co-enzymes. An initial fast half life is followed by a prolonged phase of renal excretion and a long terminal half life [24]. Severe toxicity is manifested by myelosuppression, oropharyngeal ulceration and diarrhea. Gastrointestinal side effects, especially with high-dose administration, may be expected. Serious nausea, vomiting, diarrhea, or stomatitis may result in symptomatic dehydration. Other frequently reported gastrointestinal side effects include gingivitis, pharyngitis, stomatitis, anorexia, hematemesis, melena, gastrointestinal ulceration and bleeding (Table 1). Extremely rare cases of colitis and toxic megacolon have been associated with the use of methotrexate. Gastrointestinal symptoms are often eliminated by folate supplementation which does not affect the efficacy of methotrexate [25]. High-dose methotrexate therapy results in acute aminotransferase elevation that is transient, reversible, and, at least in children, does not result in chronic liver disease. Chronic hepatotoxicity typically develops only after chronic use of higher doses and is more likely in patients who ingest ethanol, who are aged, obese, with renal insufficiency or diabetics [26].

Alkylators

The chemotherapeutic alkylating agents have the property of undergoing strongly electrophilic chemical reactions through the formation of carbonium ion intermediates or of transition complexes with the target molecules. The cytotoxic and other effects of the alkylating agents are directly related to the alkylation of components of DNA [27].

Mechlorethamine has gastrointestinal side effects including nausea and vomiting which are dose limiting. Nausea and vomiting usually occur 1-2 h after dosage administration. Emesis may disappear in the first 8 h, but nausea may persist for 24 h. They may be so severe as to precipitate vascular accidents in patients with a hemorrhagic tendency [28]. Anorexia and diarrhea have also been reported. Hepatic metabolism of mechlorethamine is not considered important and does not cause hepatic abnormalities, presumably because of its rapid degradation (Table 1).

Melphalan is another bifunctional alkylating agent and is a phenylalanine derivative of mechlorethamine. Gastrointestinal disturbances such as nausea and vomiting, diarrhea and oral ulceration occur infrequently. At usual doses, melphalan is not associated with hepatotoxicity, but it does produce transient abnormalities in liver function tests at the high doses used in autologous bone marrow transplantation. It is also related

with clinical manifestations such as hepatitis and hepatic veno-occlusive disease [29].

Chlorambucil is a close structural congener of melphalan. It is almost completely absorbed when given by the oral route and is used either continuously or intermittently for long periods [30]. Gastrointestinal side effects including nausea, vomiting, diarrhea, and oral ulceration occur infrequently [31]. Cyclophosphamide differs from the previously described alkylating agents because it is a pro-drug, requiring activation to develop cytotoxicity. It undergoes a complex multi-step activation process, being initially metabolized by the cytochrome P450 system in the liver and eventually converted to a variety of active metabolites [32,33]. Like all alkylating agents, there is a risk of developing second malignancies [34]. Nausea and vomiting commonly occur with cyclophosphamide therapy and, less frequently, abdominal discomfort or pain and diarrhea. There are isolated reports of hemorrhagic colitis and oral mucosal ulceration occurring during the therapy which are eliminated when the treatment is discontinued [35,36]. Although it has hepatic metabolism, cyclophosphamide can be given in the face of elevated liver enzymes and/or bilirubin. In spite of its requirement for hepatic metabolism for activity, cyclophosphamide is an uncommon hepatic toxin, and only a few reports of elevated hepatic enzymes are attributed to the drug.

Ifosfamide is a structural analogue of cyclophosphamide, which exhibits a similar spectrum of activity but different pharmacological properties and toxicity profile. Risk factors for the development of neurotoxicity are impaired renal or hepatic function [37,38]. Gastrointestinal side effects may be expected in most patients. Nausea or vomiting has been reported in 60-80% of patients receiving standard doses and up to 100% of patients receiving high doses. These problems may be seen a few hours after administration, typically are controlled by good antiemetic therapy and usually last only up to three days. Other gastrointestinal side effects include anorexia, diarrhea, constipation, mucositis and stomatitis (Table 1) [39] .

Carmustine and lomustine are nitrosoureas, lipid soluble which easily cross the blood-brain barrier [40]. Nausea and vomiting generally appear within 2 h of dosing and last for 4-6 h. Carmustine induced liver abnormalities have been reported in up to 26% of patients. Elevations of serum aminotransferases, alkaline phosphatase, and/or bilirubin are usually mild and revert to normal over a brief period [41]. The effects of lomustine are similar (Table 1).

Mitomycin C is related to the anthracycline anti-tumor antibiotics but differs substantially because it is the prototype bioreductive agent, undergoing preferential activation in the hypoxic environment found in solid cancers [42,43]. Gastrointestinal side effects include anorexia, nausea, vomiting and diarrhea [44].

Dacarbazine (DTIC) was initially thought to function as an anti-metabolite, given that its genesis was as an analogue of a purine precursor. However, it is now thought to be hepatically activated to function as an alkylating agent [45,46]. Frequent gastrointestinal side effects include anorexia, nausea, and vomiting which begin within 1-12 h of dosage administration. Over 90% of patients are affected within the first few doses. Vomiting has been reported to last 1-2 h [47]. Dacarbazine is metabolized by the hepatic microsomal pathway, and it has been suggested that patients with abnormal liver function may be at increased risk for hematologic toxicity. Procarbazine is metabolically activated in the liver microsomes into a DNA-methylating species and has similar side effects [48]. Gastrointestinal side effects consisting of nausea and vomiting are common and occur with initial drug administration. Procarbazine has been implicated as a cause of granulomatous hepatitis. Stomatitis, hematemesis, melena, diarrhea, dysphagia, anorexia, abdominal pain, constipation, and dry mouth have also been reported (Table 1) [49].

Targeted agents

The development of a tumor can be the result of one or several of the following alterations in cell physiology: growth signal self-sufficiency, insensitivity to growth-inhibitory signals, evasion of apoptosis, an unlimited replicative potential, sustained angiogenesis, tissue invasion, and metastasis [50]. New treatments that target the different pathways that regulate these processes have been developed. Agents that block a specific molecular target have been proven beneficial in the treatment of several tumor types and are now widely used. These compounds also exert activity on normal cells that express the molecular target, thus giving rise to adverse effects with broad spectrum. The cutaneous, hepatic or gastrointestinal adverse effects might be alternate markers of the treatment efficacy of these agents.

Diarrhea can be a major cause of treatment discontinuation and of decreased drug efficacy because it represents a dose limiting toxic event. The pathophysiological mechanism of diarrhea induced by targeted therapies remains unclear. EGFR is frequently overexpressed in gastrointestinal normal mucosa. There is evidence that EGFR is a negative regulator of chloride secretion [51]. EGFR inhibitors could, therefore, increase chloride secretion and thereby inducing secretory diarrhea. No correlation was observed between plasmatic exposure and diarrhea, whereas frequency of diarrhea is known to be dose-related [52]. These results suggest direct damage from erlotinib (Table 2). The median time to onset of the first symptoms of diarrhea with sorafenib treatment is generally short, and occurs within the first week after initiation of treatment. Most of these diarrhea episodes are moderate in severity [53]. Diarrhea usually resolves within a few days after cessation of treatment with sorafenib and is often observed during the first treatment cycle with oral anti-EGFR tyrosine kinase inhibitor compounds (Table 2) [54]. The median time to the first diarrhea episode is nearly 14 days, but the time of onset can vary widely. Diarrhea episodes are generally well controlled with administration of loperamide (Table 3) [55]. Imatinib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor, KIT and the BCR-ABL oncoprotein. It has been shown that the incidence of diarrhea is dose-related (Table

Table 2 Targeted agent, gastrointestinal toxicity, incidence, and histology

Targeted agent	Gastrointestinal toxicity	Prevalence	Histology
Gefitinib-Erlotinib	Diarrhea	54%	
	Nausea	33%	
	Vomiting	23%	
	Stomatitis	17%	
	Abdominal pain	11%	
	Transaminases elevation	2-4%	
	Gastrointestinal perforation, bleeding	infrequently	
Imatinib	Nausea	47-68%	Severe hepatitis, cytolysis
	Vomiting	21-49%	consisting of spotty necrosis
	Diarrhea	33-49%	with mild cholestasis
	Dyspepsia	9-19%	
	Abdominal pain	20-30%	
	Anorexia	3-10%	
	Constipation	4-13%	
	Gastrointestinal hemorrhage	0.2-5%	
	Mouth ulceration		
	Gastritis, gastric ulcer	infrequently	
	Transaminases elevation	1.1-3%	
	Bilirubin elevation	0.4-3.5%	
Bortezomib	Nausea	64%	Portal vein thrombosis
	Diarrhea	51%	
	Constipation	43%	
	Anorexia	43%	
	Vomiting	36%	
	Abdominal pain	14%	
	Dyspepsia	13%	
	Ascites	21%	
	Hemorrhagic gastritis	21%	
	Paralytic ileus	21%	
	Hyperbilirubinemia		
	Cholestasis		
Temsirolimus	Mucositis	41%	
	Nausea	37%	
	Anorexia	32%	
	Diarrhea	27%	
	Abdominal pain	21%	
	Constipation	20%	
	Vomiting	19%	
Sunitinib-Sorafenib	Diarrhea	66%	Centrilobular necrosis with
	Nausea	58%	moderate to severe steatosis
	Mucositis / stomatitis	53%	
	Dyspepsia	46%	
	Vomiting	39%	
	Abdominal pain	39%	
	Constipation	34%	
	Glossodynia	11%	
	Lipasemia	56%	
	Amylasemia	35%	
	Transaminasemia (SGOT)	72%	
	Transaminasemia (SGPT)	61%	
	Hyperbilirubinemia	37%	

Targeted agent	Gastrointestinal toxicity	Prevalence	Histology
Bevacizumab	Vomiting	52%	
	Anorexia	43%	
	Constipation	40%	
	Diarrhea	34%	
	Stomatitis	32%	
	Dyspepsia	24%	
	Gastrointestinal hemorrhage	24%	
	Colitis	6%	
	Gastrointestinal perforation / fistula formation	0.9-2.4%	

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase

2) [56,57]. In patients with gastrointestinal stromal tumors, independent risk factors for diarrhea were high imatinib dose, female sex, and the primary site of gastrointestinal disease [56]. The proteasome inhibitor bortezomib frequently induces watery diarrhea with no bleeding, but treatment with this drug is often associated with abdominal pain and cramps (Table 2). The abdominal symptoms seen with bortezomib are mild to moderate, dose-dependent and time-dependent, start within 12-18 h after infusion initiation and last 1-2 days [58,59]. Temsirolimus, an mTOR inhibitor with immunosuppressive properties, might cause fecal alterations with mucoid feces and colitis, secondary to an immunosuppressive or an antimicrobial effect, leading to altered microbial flora in the bowel (Table 2). Another surprising mechanism has been suggested by a non-randomized study, which showed that low-dose aspirin was able to reduce gefitinib-induced adverse events including diarrhea by inhibiting platelet activation [60]. There was a marked increase following aspirin administration in some platelet-related factors such as thromboxane A2 in patients treated with gefitinib. Thromboxane A2 is an endogenous secretagog of chloride secretion in the distal colon [61]. It is possible, therefore, that gefitinib could induce diarrhea by increasing some inflammatory mediators as a secondary response to activation of cell immunity (Table 2).

Hepatotoxicity is the second common cause of discontinuation of treatment with imatinib [62]. Hepatic adverse effects, such as asymptomatic elevations of transaminases are examples of other common toxic events associated with molecular-targeted therapies. Some compounds also increase γ-glutamil transpeptidase or bilirubin levels, which reflects enzyme induction. Actually, an interaction with hepatic membrane transporters might alter the absorption of unconjugated bilirubin [63]. Rising transaminase levels are often observed within the first 3 months of imatinib treatment but can occur much later, even after 1 year of therapy. When imatinib is ceased, abnormalities often resolve within 3 weeks and enzyme elevation often occurs after several months (Table 2). Histological findings of acute liver failure with imatinib demonstrate cytolytic hepatitis with necrosis, and sometimes mild cholestasis with portal and lobular inflammation [64]. Many cases of hepatitis following imatinib therapy have been observed [65,66]. A similar pattern of viral hepatitis with lymphocyte infiltration around the necrotic lesions has been reported (Table 2) [67]. Severe cytolytic hepatitis with gefitinib has also been described [68]. Most molecular-targeted cancer agents are metabolized in the liver via the cytochrome pathway. Drug-induced stress can give rise to an increase in heat-shock proteins, ensuring spontaneous normalization of liver abnormalities, which suggests a direct toxic effect. It has been suggested that there is a link between hepatotoxicity and serum concentrations of drugs, such as imatinib [69]. Moreover, the severity of toxic effects can be increased when imatinib is taken with a CYP3A4 inhibitor such as roxithromycin [70]. Hypersensitivity reactions with immune-mediated drug reactions could be involved in hepatic adverse effects. In this aspect imatinib may induce autoimmune hepatitis (Table 2) [71]. It also could worsen an underlying prothrombotic status by damaging endothelial cells, especially in the liver. Biopsy samples showed evidence of fibrin thrombi in hepatic veins, but microscopic emboli were also detected in the lungs [72]. In current practice, imatinib therapy is interrupted when patients exhibit hepatotoxicity of grade 3 or 4 transaminase elevation. When abnormalities return to grade 1 or less, imatinib can be reintroduced at a reduced dose. If the liver toxic effects do not recur within 6-12 weeks, the initial dose can be re-escalated, accompanied by close monitoring by use of liver function tests (LFTs). For recurrent grade 3 toxicity, guidelines recommend discontinuation of imatinib [73]. Patients taking molecular-targeted cancer drugs should avoid a further hepatotoxic compound such as alcohol or paracetamol. Coadministration of steroids and gefitinib to patients who have experienced previous hepatic reactions has led to hepatotoxicity. By contrast, steroids were able to resolve imatinib-induced hepatic toxic effects in a few patients [74]. Sorafenib and sunitinib can induce hyperlipasemia and hyperamylasemia (Table 2). As it is cleared primarily by the liver, it is possible that erlotinib exposure may be increased in patients with hepatic dysfunction. These abnormalities are not observed with the anti-VEGF monoclonal antibody bevacizumab, anti-EGFR therapies or other oral antiangiogenic compounds. It is well described the protective effect of bevacizumab

Table 3 Drug, gastrointestinal toxicity, and management

Drug	Gastrointestinal toxicity	Management [4,97-99]
Docetaxel, Paclitaxel, Carboplatin, Oxaliplatin, Doxorubicin, Imatinib, Cytarabine, Cyclophosphamide, Ifosfamide	Vomiting (High - Moderate emetogenicity)	Serotonin (5-HT3) receptor antagonists Ondansetron Oral: 24 mg i.v.: 8 mg or 0.15 mg/kg Granisetron Oral: 2 mg i.v.: 1 mg or 0.01 mg/kg Tropisetron Oral or i.v.: 5 mg Dolasetron Oral: 100 mg i.v.: 100 mg or 1.8 mg/kg Palonosetron i.v.: 0.25 mg Dexamethasone Oral: 12 mg Oral: 20 mg[a] Aprepitant Oral: 125 mg
Docetaxel, Paclitaxel, Oxaliplatin, Gefitinib, Erlotinib, Bortezomib, Sunitinib, Cytarabine and Targeted agents	Diarrhea	Loperamide 4 mg initially taking 2 mg, after each subsequent bowel movement, to a max dose of 8 mg in 24 h Codeine phosphate 30 mg instead of loperamide or added to loperamide when control is not achieved with loperamide alone Octreotide 100150 mcg injected 3 times daily up to 500 mcg
Fluoropyrimidines	Diarrhea-Mucositis	Dose limiting, aggressive hydration Loperamide 4mg initially taking 2mg, after each subsequent bowel movement, to a max dose of 8 mg in 24 h Octreotide 100150 mcg injected 3 times daily up to 500 mcg
Docetaxel, Oxaliplatin, Doxorubicin, Bevacizumab, Cytarabine, Gemcitabine, Methotrexate, Chlorambucil, Targeted agents	Stomatitis	Topical fluoride tooth brushing, flossing analgesia with morphine. For prevention are used: amifostine, azelastine, chamomile, chlorhexidine, clarithromycin, povidone iodine, prostaglandin E2 analog For treatment: clindamycin, nonsteroidal anti-inflammatory drugs, tobramycin, anphotericin, glautamine
Docetaxel, Paclitaxel	Colitis	Aggressive fluid resuscitation, antiperistaltic agents, bowel rest, broad antibiotic coverage (metronidazole, ciprofloxacin, vancomycin)

[a]*20mg if aprepitant is not available. If dexamethasone is not available limited data suggest that prednisolone or methylprednisolone can be substituted at doses about 7 and 5 times higher respectively*

against sinusoidal injuries induced by oxaliplatin-based chemotherapy and is shown not to impair liver regeneration following portal vein embolization. Elevation of pancreatic enzymes might be an immunoallergic reaction or a marker of the drug bioactivity. It is not clear whether these effects are caused by pancreatitis. Abdominal pain and lipase elevation threefold above the upper limit of normal are required for the diagnosis of pancreatitis (Table 2). If lipasemia elevation occurs (above twofold the upper limit of normal), treatment with imatinib must be discontinued until the serum level of enzymes returns within normal values.

Several cases of gastrointestinal perforation have been reported in patients treated with bevacizumab and chemotherapy. The Bevacizumab Regimens Investigation of Treatment Effects and Safety (BRiTE) registry reported gastrointestinal perforation in 1.7% of 1,987 patients with metastatic colorectal cancer [75]. The clinical pattern and severity of perforation seen was variable, ranging from

asymptomatic to fatal perforations. Most gastrointestinal perforations occurred within the first 3 months after initiation of treatment. The incidence of perforations was greatest in cases of an intact primary tumor or a recent history of sigmoidoscopy or colonoscopy. On the other hand, long-term use of nonsteroidal anti-inflammatory compounds or a history of peptic ulcer disease or diverticulosis was not associated with a high risk of gastrointestinal perforation. A rapid response to molecular-targeted cancer drugs could be associated with toxic effects and necrosis as evidenced by perforation [57]. It has also been suggested that treatment with bevacizumab following radiation of the pelvis might increase the risk of ischemic bowel damage (Table 2) [76]. Discontinuation of the regimen in patients who experience such adverse effects is mandatory.

Pathophysiology and principles of management of gastrointestinal toxicity

Chemotherapy-induced nausea and vomiting has been cited as the most concerning symptom after administration of chemotherapy [77]. It varies from slight nausea to protracted vomiting with subsequent dehydration. Chemotherapy stimulates the release of serotonin from the enterochromaffin cells lining the gastrointestinal tract. Serotonin stimulates type-3 vagal afferent serotonin receptors (5-HT3) located in the gastrointestinal tract, the nucleus tractus solitarius of the medulla oblongata and the chemoreceptor trigger zone which lies outside the blood-brain barrier and sends impulses to the vomiting center when stimulated by an emetogenic substance [78]. Acute nausea and vomiting is subjectively defined to occur within 24 h of administration of emetogenic chemotherapy. The type of chemotherapy as well as the dose and administration has an impact on the severity or risk of acute emesis. The serotonin antagonists have the most significant activity in the treatment of acute nausea and vomiting associated with cisplatin [79]. They block 5-HT3 receptors in the central nervous system (CNS) as well as the vagal periphery resulting in significant reductions in acute nausea induced by chemotherapy [80]. Currently, ondansetron, granisetron, and dolasetron are available as choices of this category (Table 3). The side effect profile is similar for all of these agents. Headache is the most common side effect, followed by an asymptomatic prolongation of electrocardiographic interval [78]. Dexamethasone was found to improve efficacy when added to metoclopramide, so researchers tested it in combination with ondansetron. A study by Roila et al revealed that by combining dexamethasone with ondansetron the antiemetic response was improved by as much as 27% [81]. Delayed emesis occurs 24 h or more after chemotherapy has been administered. This effect can be observed for as many as 5 days after treatment. Delayed nausea and vomiting from chemotherapy is a symptom that is not easily treated. Corticosteroids, such as dexamethasone, have an unknown mechanism of action but have been shown, thus far, to have the best effectiveness against delayed emesis. The use of oral dexamethasone plus metoclopramide has been given a high level of support for reduction in delayed emesis because of cisplatin (Table 3) [82,83].

The pathophysiology of diarrhea is extensive, complex and likely to be the result of a number of mechanisms. A number of different types of diarrhea can be directly related to cancer treatments, such as secretory, osmotic, malabsorption, exudative and dysmotility [84]. Other types of diarrhea are recognized and may be related to cancer therapies and these include infectious, inflammatory and steatorrhea. Loperamide is often the first drug that is used to control symptoms and functions by decreasing intestinal motility by directly affecting the smooth muscle of the intestine (Table 3) [85,86]. Octreotide is another potential drug that may reduce diarrhea (Table 3) [87]. It works by acting on the epithelial cells, inhibiting gut hormones such as serotonin, vasoactive intestinal peptide and gastrin, as well as increasing intestinal transit time [88]. In conclusion, the management of diarrhea caused by treatment therapy has three main aims. Decreasing the volume of diarrhea induced, treating all dehydration aggressively and treating patient with antibiotics if symptoms were prolonged and/or if patient had accompanying neutropenia [89].

Hepatotoxicity is of greater concern, and altered hepatic clearance may cause increased non hepatic toxicity. Cisplatin-induced acute hepatic injury is dose-related. There is no correlation between the cumulative dose of oxaliplatin and the presence or intensity of the sinusoidal injury. Hepatotoxicity from 5-FU appears to be both time- and dose-dependent. With rare exceptions, the hepatitis picture usually improves with the temporary cessation of chemotherapy, but the development of secondary sclerosing cholangitis is irreversible. Modification of the dosage of procarbazine in the face of hepatic dysfunction is probably advisable. Intermittent schedule of gefitinib administration not only successfully reduced hepatotoxicity but also induced disease regression. Dose reduction or interruption of erlotinib should be considered if changes in liver function are severe. Recurrent severe hepatotoxicity requires permanent discontinuation of imatinib. As it is mentioned, introduction of corticosteroids capacitate successful continuation of imatinib therapy. The combined clinical application will require a careful adjustment of the currently used bortezomib dose. Sunitinib should be interrupted for grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Sunitinib should not be restarted if patients subsequently experience serious changes in liver function tests or have other signs and symptoms of liver failure.

Conclusions

Nausea and vomiting are the most common distressing early toxic features of cytotoxic agents, whereas treatment-induced gastrointestinal mucositis leads to compromise of the mucosal barrier and ulceration, resulting in systemic

infection in more than 70% of patients receiving myeloablative or myelosuppressive therapy [90]. Diarrhea and constipation are manifestations of alimentary mucositis, a condition which affects the entire gastrointestinal tract [91]. The changes in the composition of the microflora result in absorption and other intestinal function dysregulation [91]. On the other hand, the mechanisms underlying chemotherapy induced constipation remain poorly defined. Often it is secondary to drugs that are given to control other chemotherapy- or cancer-induced symptoms such as antiemetics and opioids [92].

Patients who are to receive chemotherapy require careful assessment of liver function prior to treatment. Liver injury during cancer chemotherapy may not always reflect hepatotoxic anticancer drugs. The clinician must also consider reactions to antibiotics, analgesics, antiemetics, or other medications [93]. Preexisting medical problems, tumor, immunosuppression, hepatitis viruses and other infections may affect a host's susceptibility to liver injury [94]. Toxic liver lesion can reproduce almost any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury.

Age-related differences in pharmacokinetics can increase the toxicity of antineoplastic drugs and their metabolites. Over time, the body progressively accumulates more fat, and this can alter drug distribution in older persons. Higher proportions of body fat may increase the volume of distribution of lipid-soluble drugs, but other changes, such as reduced total body water and reduced concentrations of plasma proteins and hemoglobin may decrease the volume of distribution and increase the plasma concentrations of hydrophilic drugs [95]. The reduction in serum albumin concentration in older adults results in an increase in the unbound fraction of some drugs, which may have important implications for the distribution of drugs bound to albumin. Studies had shown that low serum albumin concentrations in malnourished older patients with advanced cancer resulted in a low clearance of highly albumin-bound drugs which, in turn, caused increased free drug concentration and contributed to unexpected toxicity [96]. Because several of the common chemotherapeutic agents bind to red blood cells, the influence of hemoglobin levels on drug toxicity is of particular interest. For those drugs that are highly bound to red blood cells, such as taxanes and anthracyclines, anemia is associated with a greater concentration of free drug in the circulation, and it is an independent risk factor for myelosuppression.

Weight loss in cancer patients is accompanied by a loss of fat as well as by enhanced plasma levels of triglycerides. Lipid oxidation can be normal or increased. What causes the alterations in lipid metabolism remains unclear. However, increased lipolysis is frequently observed.

Predicting toxicity often is difficult because of patient variation in drug metabolism and the narrow therapeutic window of most chemotherapeutic agents. In this aspect, clinicians have made an effort to "normalize" the drug dose. The current method of drug normalization is the use of body surface area (BSA), which is derived from patients' height and weight. The BSA does not take into account the fat, protein, and water levels of the patient's body at the time of chemotherapy.

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