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

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.

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
| Drug                  | Gastrointestinal toxicity                  | Prevalence | Histology                              |
|----------------------|-------------------------------------------|------------|----------------------------------------|
| **Taxanes**          | Nausea                                    | 40%        | Ischemic colitis, neutropenic colitis,  |
|                      | Diarrhea                                  | 37-40%     | ischemia with venous thromboses within  |
|                      | Vomiting                                  | 25%        | the wall of the bowel                  |
|                      | 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** | Vomiting < 60 mg/m²                         | 60-90%     | Perisinusoidal fibrosis, hepatocytes show atrophic changes |
| (cisplatin, carboplatin) | Vomiting > 60 mg/m²                        | > 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%        |                                        |
| **Anthraclyclines**  | 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                       | 50%        |                                        |
|                      | Diarrhea                                  | 44%        |                                        |
|                      | Anorexia                                  | 44%        |                                        |
|                      | Nausea                                    | 26%        |                                        |
|                      | Vomiting                                  | 34%        |                                        |
|                      | Proctitis                                 |            |                                        |
|                      | Mucositis                                 |            |                                        |
|                      | Hyperbilirubinemia                        |            |                                        |
| **Cytarabine, Gemcitabine** | Oral and anal inflammation or ulceration | frequently | Necrotizing colitis, veno-occlusive disease |
|                      | Anorexia                                  | frequently |                                        |
|                      | Nausea                                    | frequently |                                        |
|                      | Vomiting                                  | frequently |                                        |
|                      | Diarrhea                                  | frequently |                                        |
|                      | Bowel necrosis                            | frequently |                                        |
|                      | Stomatitis                                |             |                                        |
|                      | Pancreatitis                              |             |                                        |
|                      | Hepatic dysfunction                       |             |                                        |
| Drug                  | Gastrointestinal toxicity                              | Prevalence | Histology                                                                 |
|----------------------|--------------------------------------------------------|------------|---------------------------------------------------------------------------|
| Methotrexate         | Nausea                                                 | 10-80%     | Macrosteatosis, fibrosis, fatty change, focal hepatitis, cirrhosis,       |
|                      | Vomiting                                               | 10-80%     | low grade portal inflammation, hepatocellular carcinoma (case reports)    |
|                      | Diarrhea                                               | 10-80%     |                                                                           |
|                      | Stomatitis                                             | 10-80%     |                                                                           |
|                      | Pharyngitis                                            | 10-80%     |                                                                           |
|                      | Anorexia                                               | 10-80%     |                                                                           |
|                      | Melena                                                 | 10-80%     |                                                                           |
|                      | Gastrointestinal ulceration                            |            |                                                                           |
|                      | Enteritis                                              |            |                                                                           |
|                      | Elevations of aminotransferases and serum lactate      | 14.1%      |                                                                           |
|                      | dehydrogenase                                          |            |                                                                           |
|                      | Acute hepatitis                                         |            |                                                                           |
|                      | Chronic fibrosis                                        |            |                                                                           |
|                      | Cirrhosis                                              |            |                                                                           |
|                      | Decrease in serum albumin                              |            |                                                                           |
|                      | Nausea and vomiting                                    | 70-90%     | Massive hepatic necrosis, necrosis of perivenous hepatocytes and diffuse  |
|                      | Anorexia                                               | Less frequently | diffuse hepatocellular damage with mild steatosis                      |
|                      | Abdominal discomfort, pain                             | Less frequently |                                                                           |
|                      | Diarrhea                                               | Less frequently |                                                                           |
|                      | Hemorrhagic colitis                                     | Less frequently |                                                                           |
|                      | Elevated hepatic enzymes                                | Few reports |                                                                           |
|                      | 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%       |                                                                           |
|                      | Increased transaminases, ALP an bilirubin levels        |            |                                                                           |
|                      | Nausea and vomiting                                    | 35%        | Granulomatous hepatitis with tissue eosinophilia                        |
|                      | Anorexia                                               | Infrequently |                                                                           |
|                      | Stomatitis                                             | Rare        |                                                                           |
|                      | Mucositis                                              | rare        |                                                                           |
|                      | Increased transaminases, ALP an bilirubin levels        | In a small percentage of patients |                                                                           |
|                      | Melena                                                 |            |                                                                           |
|                      | Diarrhea                                               |            |                                                                           |
|                      | Anorexia                                               |            |                                                                           |
|                      | Stomatitis                                             |            |                                                                           |
|                      | Mucositis                                              |            |                                                                           |
|                      | Increased transaminases, ALP an bilirubin levels        |            |                                                                           |
|                      | 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].
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/m² 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 nephotoxic 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, hemoptyisis, 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.

Cytarabine 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 disseminated 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 follow 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 heptatically 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 oncprotein. It has been shown that the incidence of diarrhea is dose-related (Table 2 of 111).
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, bleeding                      | 2-4%       |                                               |
| 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%      |                                               |
|                        | Gastrintestinal hemorrhage                             | 0.2-5%     |                                               |
|                        | Mouth ulceration                                       | infrequently|                                               |
|                        | 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 moderate to severe steatosis |
|                        | Nausea                                                 | 58%        |                                               |
|                        | 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%        |                                               |
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 secretagogue 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-glutamyl 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 cytolysis 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 cytolysis 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 |
| | | 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) |

*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 immunologic 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 hepatoxic 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.

References

1. Bonaventura A. Complications of cytotoxic therapy. Australian Prescriber 1995;18:66-67.
2. Rubenstein E, Peterson D, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer chemotherapeutic agent-induced oral and gastrointestinal mucositis. Cancer 2004;100:2026-2046.
3. Wood KW, Cornwell WD, Jackson JR. Past and future of the mitotic spindle as an oncology target. Curr Opin Pharmacol 2001;1:370-377.
4. Li Z, Ibrahimi NK, Wathen JK, et al. Colitis in patients with breast carcinoma treated with Taxane-based chemotherapy. Cancer 2004;101:1508-1513.
5. Jamieson ER, Lippard SJ. Structure, recognition and processing of Cisplatin-DNA adducts. Chem Rev 1999;99:2467-2498.
6. Sheikh-Hamad D, Timmins K, Jalali Z. Cisplatin-induced renal toxicity: Possible reversal by N-Acetylcysteine treatment. J Am Soc Nephrol 1997;8:1640-1645.
7. Hesketh PJ, Kris MG, Grünberg SM, et al.Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
8. Markman M, Zanotti K, Webster K, Belinson J, Rose P. Toxicity associated with carboplatin/paclitaxel/irinotecan use in advanced ovarian cancer: preliminary analysis. Oncology (Williston Park) 2003;17:34-35.
9. Cassidy J, Misset JL. Oxaliplatin-related side effects: characteristics and management. Semin Oncol 2002;2:11-20.
10. Turek-Plewa J, Jagodzinski PP. The role of mammalian DNA methyltransferases in the regulation of gene expression. Cell Mol Biol Lett 2005;10:631-647.
11. Parnham MJ, Bruinvels J. Milestones in Drug Therapy. In: Pinelo HM and Smorenburg CH (editors): Drugs affecting growth of tumours. Birkhäuser Verlag. Basel, Switzerland:2006:19-81.
12. Bardos TJ. Topics in current chemistry. In: Boschke FL (editor): Antimetabolites: Molecular design and mode of action. Springer Verlag. Berlin; 1974:63-98.
13. Longley DB, Harkin DR. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer 2003;3:330-338.
14. Rougier P, Paullot B, Laplanche A, et al. 5-Fluorouracil (5-FU) continuous intravenous infusion compared with bolus administration. Final results of a randomised trial in metastatic colorectal cancer. Eur J Cancer 1997;33:1789-1793.
15. McCollum AD, Catalano P, Haller D. Outcomes and toxicity associated with carboplatin/paclitaxel/irinotecan use in advanced ovarian cancer: preliminary analysis. Oncology (Williston Park) 2002;14:1160-1167.
16. Reignier B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 2001;40:85-104.
17. Walko CM, Lindley C. Capecitabine: a review. Clin Ther 2005;27:23-44.
18. Saler JS, Balis ME. The mechanism of action of 6 Mercaptopurine. In: Boschke FL (editor): Topics in current chemistry. In: Pinelo HM and Smorenburg CH (editors): Drugs affecting growth of tumours. Birkhäuser Verlag. Basel, Switzerland:2006:19-81.
19. Katsanos KH, Tsianos EV. Azathioprine/6-mercaptopurine toxicity: Possible reversal by N-Acetylcysteine treatment. J Am Soc Nephrol 1997;8:1640-1645.
20. Yamauchi T, Negoro E, Kishi S, et al. Intracellular cytarabine triphosphate production correlates to deoxycytidine kinase/ cytosolic 5’-nucleotidase II expression ratio in primary acute myeloid leukemia cells. Biochem Pharmacol 2009;77:1780-1786.
21. Tenstoft J. The toxicity of cytarabine. Drug Saf 1990;5:7-27.
22. Plunkett W, Huang P, Xu YZ, et al. Gemcitabine: metabolism, mechanisms of action, and self-potentiation. Semin Oncol 1995;22:1-10.
23. Vander Els NJ, Miller V. Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. Chest 1998;114:1779-1781.
24. Hryniuk WM. The Mechanism of action of Methotrexate in cultured L5178Y leukemia cells. Cancer Res 1975;35:1085-1092.
25. Ortiz Z, Shea B, Suarez-Almazor ME, Moher D, Wells GA, Tugwell P. The efficacy of folic acid and folinic acid in reducing methotrexate gastrointestinal toxicity in rheumatoid arthritis. A metaanalysis of randomized controlled trials. J Rheumatol 1998;25:36-43.
26. Schiemann U, Kellner H. Gastrointestinal side effects in the therapy of rheumatologic diseases. Z Gastroenterol 2002;40:937-943.
27. Lawley PD, Phillips DH. DNA adducts from chemotherapeutic agents. Mutation Res 1996;355:13-40.
28. Solimando DA. Mechloretamine and procarbazine. Hospital Pharmacy 1998;33:1300-1304.
29. Cunningham D, Paz-Ares L, Gore ME, et al. High-dose melphanal for multiple myeloma: long-term follow-up data. J Clin Oncol 1994;12:764-768.
30. Bank BB. Studies of chlorambucil-DNA adducts. Biochem Pharmacol 1992;44:571-575.
31. Electronic Medicines Compendium (5th Edition) http://emc.vhn.net/ Dec 2005.
32. Chen CS, Lin JT, Goss KA, et al. Activation of the anticancer prodrugs cyclophosphamide and ifosfamide: identification of cytochrome P450 2B enzymes and site-specific mutants with improved enzyme kinetics. Mol Pharmacol 2004;65:1278-1285.
33. Schilsky RL. Renal and metabolic toxicities of cancer chemotherapy. Semin Oncol 1982;9:75-83.
34. Watanabe Y, Etoh M, Koike E, Mizuno Y, Wang WM, Hoshiai H. Acute and long-term toxicity of cyclophosphamide. Tx Med 2007;19:26-31.
35. Klastersky J. Side effects of ifosfamide. Leukemia 1996;10:347-351.
36. Van Glabbeke M, Verweij J, Casali PG, et al. Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). Eur J Cancer 2006;42:2277-2285.
37. Demetri GD, Von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumours. N Engl J Med 2002;347:472-480.
38. Papandreu CN, Dalliani DD, Nix D, et al. Phase I of the proteasome inhibitor bortezomib in patients with advanced solid tumours with observations in androgen-independent prostate cancer. J Clin Oncol 2004;22:2108-2121.
39. Armand JP, Ribrag V, Harrousseau JL, Abrey L. Reappraisal of the use of procarbazine in the treatment of lymphomas and brain tumours. Ther Clin Risk Manag 2007;3:213-224.
40. Uribe JM, Gelbmann CM, Traynor-Kaplan AE, Barrett KE. Epidermal growth factor inhibits calcium-dependent chloride secretion in T84 human colonic epithelial cells. Am J Physiol Cell Physiol 1996;271:914-922.
41. Lu JF, Eppler SM, Wolf J, et al. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. Clin Pharmacol Ther 2006;80:136-145.
42. Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of the Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell cancer. J Clin Oncol (Meeting Abstracts) 2005;23(Suppl 16):LBA4510.
43. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006;295:2516-2524.
44. Uribe JM, Gelbmann CM, Traynor-Kaplan AE, Barrett KE. Epidermal growth factor inhibits calcium-dependent chloride secretion in T84 human colonic epithelial cells. Am J Physiol Cell Physiol 1996;271:914-922.
45. Lawley PD, Phillips DH. DNA adducts from chemotherapeutic agents. Mutation Res 1996;355:13-40.
46. Schiemann U, Kellner H. Gastrointestinal side effects in the therapy of rheumatologic diseases. Z Gastroenterol 2002;40:937-943.
47. Lawley PD, Phillips DH. DNA adducts from chemotherapeutic agents. Mutation Res 1996;355:13-40.
48. Schiemann U, Kellner H. Gastrointestinal side effects in the therapy of rheumatologic diseases. Z Gastroenterol 2002;40:937-943.
49. Lawley PD, Phillips DH. DNA adducts from chemotherapeutic agents. Mutation Res 1996;355:13-40.
treatment: CASE 1. Hepatitis following treatment with gefitinib. J Clin Oncol 2005;23:8531-8533.
69. Kikuchi S, Murai K, Takahashi S, et al. Severe hepatitis and complete molecular response caused by imatinib mesylate: possible association of its serum concentration with clinical outcomes. Leuk Lymphoma 2004;45:2349-2351.
70. James C, Trouette H, Marit G, Cony-Makhoul P, Mahon FX. Histological features of acute hepatitis after imatinib mesylate treatment. Leukemia 2003;17:978-979.
71. Dhalluin-Venier V, Besson C, Dimet S, Thirot-Bibault A, Tchernia G, Buffet C. Imatinib mesylate induced acute hepatitis with autoimmune features. Eur J Gastroenterol Hepatol 2006;18:1235-1237.
72. Lin NU, Sarantopoulos S, Stone JR, et al. Fatal hepatic necrosis following imatinib mesylate therapy. Blood 2003;102:3455-3456.
73. Deininger MW, O’Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol 2003;21:1637-1647.
74. Ferrero D, Pogliani EM, Rege-Cambrin G, et al. Corticosteroids can reverse severe imatinib-induced hepatotoxicity. Haematologica 2006;91(Suppl 6):E627.
75. Kozloff M, Cohn A, Christiansen N, et al. Safety of bevacizumab (BV) among patients (pts) receiving first-line chemotherapy for metastatic colorectal cancer: updated results from a large observational study in the US (BriTE). Gastrointestinal Cancers Symposium 2006 [abstract #247].
76. Lordick F, Geinitz H, Theisen J, Sendler A, Sarbia M. Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. Int J Radiat Oncol Biol Phys 2006;64:1295-1298.
77. Coates A, Abraham S, Kaye SB, et al. On the receiving end—patient perception of the side effects of cancer chemotherapy. Eur J Cancer Oncology 1983;19:203-208.
78. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999;56:729-764.
79. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. J Clin Oncol 1991;9:721-728.
80. Tyers MB. Pharmacology and preclinical antieptic properties of ondansetron. Semin Oncol 1992;19(Suppl 10):1-8.
81. Rolaia, Tonato M, Cognetti F, et al. Prevention of cisplatin-induced emesis: A double-blind multicenter crossover study comparing ondansetron plus dexamethasone. J Clin Oncol 1991;9:675-678.
82. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: Evidence based clinical practice guidelines. J Clin Oncol 1999;17:2971-2994.
83. Jantunen IT, Muhanen TT, Kataja VV, Flander MK, Teerenhovi L. 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy – a randomised study. Eur J Cancer 1993;29A:1669-1672.
84. Engelking C, Rutledge DN, Ippoliti C, Neumann J, Hogan CM. Cancer related diarrhea: a neglected cause of cancer-related symptom distress. Oncol Nurs Forum 1998;25:859-860.
85. Saltz L, Shimada Y, Khayat D. CPT-11 (irinotecan) and 5-fluorouracil: a promising combination for therapy of colorectal cancer. Eur J Cancer 1996;32A(Suppl 3):S24-S31.
86. Stern J, Ippoliti C. Management of acute cancer treatment-induced diarrhea. Semin Oncol Nurs 2003;19(4 Suppl 3):11-16.
87. Janssman FG, Sleijfer DT, De Graaf JC, Coenen JL, Brouwers JR. Management of chemotherapy-induced adverse effects in the treatment of colorectal cancer. Drug Saf 2001;24:353-367.
88. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(Suppl 9):2026-2046.
89. Sharma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. Lancet Oncol 2005;6:93-102.
90. Elting LS, Cookeley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burden of cancer therapy: Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 2003;98:1531-1539.
91. Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer 2006;14:890-900.
92. Portenoy RK. Constipation in the cancer patient: causes and management. Med Clin North Am 1987;71:303-311.
93. King PD, Perry MC. Hepatotoxicity of Chemotherapy. Oncologist 2001;6:162-176.
94. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003;349:474-485.
95. Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. Hematol Oncol Clin North Am 2000;14:193-212.
96. Walter-Sack I, Klotz U. Influence of diet and nutritional status on drug metabolism. Clin Pharmacokinet 1996;31:47-64.
97. Rolaia, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 2010;21(Suppl 5):232–243.
98. Benson III AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. JCO 2004;22:2918-2926.
99. Elting LS, Keefe DMK, Sonis ST. Treatment induced gastrointestinal toxicity in patients with cancer. ASCO 2005:117-123.