The Gastrointestinal Complications of Oncologic Therapy

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KEYWORDS

- Drug-induced diarrhea • Neutropenic enterocolitis
- Graft-versus-host disease
- Chemotherapy-induced nausea and vomiting • Liver injury

A spectrum of oncologic treatments including chemotherapy, radiotherapy, and molecular targeted therapies is available to combat cancer. These treatments are associated with adverse effects in several organ systems including the gastrointestinal (GI) tract. Any part of the GI tract can be affected including the upper GI tract (esophagitis due to bacterial, viral, and fungal infections; mucositis due to chemotherapy or radiation; GI bleeding; nausea and vomiting), colon (diarrhea, graft-vs-host disease [GVHD], and constipation), liver (drug toxicity and GVHD), and pancreas (pancreatitis). Adverse effects range from mild to life threatening. The primary goal of cancer treatment is to administer the most effective therapy while minimizing potential toxicity. This review discusses common GI complications that can result from cancer therapy. The pathologic mechanisms underlying each complication and the pharmacology of the agents used to treat these complications are discussed.

ESOPHAGITIS

Esophagitis in patients with cancer may be caused either by the direct cytotoxic effects of chemotherapy or radiation or by the infections caused by immunosuppressive effects of cancer therapy (**Table 1**).[1] Treatment with chemotherapy or radiotherapy destroys rapidly dividing cells, such as those in the epithelial cell layer. Cell death decreases the renewal rate of the basal epithelium, causing mucosal atrophy, ulceration, and initiation of the inflammatory response. Synergy between chemotherapy and radiotherapy may increase the severity and extent of esophagitis

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Table 1
Common causes of esophagitis in patients receiving oncologic therapy

Infectious Agent or Injury	Endoscopic Appearance	Treatment
Candida albicans	White plaquelike lesions with surrounding erythema on the esophageal mucosa	Systemic antifungal treatment with fluconazole, itraconazole, voriconazole, or echinocandins)
Herpes Simplex Virus	Small vesicles, coalescing to form ulcers	Acyclovir, foscarnet sodium
Cytomegalovirus	Linear or serpiginous ulcers	Ganciclovir, foscarnet sodium
Varicella-Zoster Virus	Small vesicles, similar to herpes simplex virus ulcers	Intravenous acyclovir
Polymicrobial Oral Flora	Bacteria mixed with necrotic epithelial cells in biopsy samples	Broad-spectrum antibiotics
Radiation Injury	Friable mucosa with erythema and edema	Lidocaine hydrochloride, proton pump inhibitors, endoscopic dilation, or stents

Data from Davila M, Bresalier RS. Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol 2008;5(12):682–96.

observed with combined therapy.[2] Esophagitis may also be caused by pill-induced injury, acid reflux disease, and GVHD in hematopoietic stem cell transplant recipients.

Fungal Infections

Esophageal candidiasis is common in immunocompromised patients, with *Candida albicans* being the most frequent causative organism for esophageal and oropharyngeal candidiasis (OPC). Patients complain of odynophagia and/or dysphagia. On endoscopy, esophageal candidiasis is identified by white plaquelike lesions with surrounding erythema. Esophageal biopsies or brushings may confirm the presence of invasive yeast or hyphal forms of *C albicans*.

An empirical course of antifungal therapy is recommended in immunocompromised patients with odynophagia or dysphagia. Endoscopy should be performed if symptoms do not improve within 72 hours.[3] The general duration of antifungal treatment is 14 to 21 days. Candida esophagitis in immunocompromised patients requires systemic antifungal therapy and cannot be treated with topical agents.[4] Patients unable to tolerate oral agents require intravenous therapy.

The treatment of esophageal candidiasis includes agents such as azoles, echinocandins, or amphotericin B. Azoles inhibit cell membrane formation by inhibiting the synthesis of ergosterol, a principal component of fungal cell membranes.[5] Fluconazole is the recommended first line agent because of its efficacy, ease of administration, and low cost.[4] For patients with fluconazole-refractory esophageal candidiasis who can tolerate oral therapy, newer azoles (voriconazole and posaconazole) are available (**Table 2**).[6,7] Itraconazole has been found to be as effective as fluconazole for the treatment of esophageal candidiasis, however, its use is limited by significant nausea and the potential for drug interactions because of the inhibition of cytochrome P-450.[8,9]

Patients requiring intravenous therapy should be treated with one of the echinocandins (caspofungin, micafungin, or anidulafungin), rather than amphotericin B, because of their better toxicity profiles.[10,11] Echinocandins inhibit synthesis of β(1,3)-D-glucan,

Table 2
Treatment of mucocutaneous candidiasis

	First Line Therapy	Alternative Therapy	Comments
Oropharyngeal Candidiasis	Clotrimazole troches; nystatin suspension or fluconazole	Itraconazole solution; or posaconazole or voriconazole or AmB-d oral suspension; IV echinocandin or AmB-d	Fluconazole is recommended for moderate to severe disease, and topical therapy with clotrimazole or nystatin is recommended for mild disease. Uncomplicated disease is treated for 7–14 d. For refractory disease, itraconazole, voriconazole, posaconazole, or AmB-d suspension is recommended
Esophageal Candidiasis	Fluconazole an echinocandin; or AmB-d	Itraconazole oral solution; or posaconazole or voriconazole	Oral fluconazole is preferred. For patients unable to tolerate an oral agent, IV fluconazole, an echinocandin, or AmB-d is appropriate. Treatment is for 14–21 d. For patients with refractory disease, the alternative therapy as listed or AmB-d or an echinocandin is recommended

Abbreviations: Amb-d, amphotericin B deoxycholate; IV, intravenous.

Data from Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48(5):503–35.

an essential component of the fungal cell wall. Mammalian cells do not require β(1,3)-D-glucan, thereby limiting potential toxicity.[10] Relapse rates are higher with echinocandins when compared with azoles, and echinocandins are used as second line therapeutic agents if treatment with azoles has failed. Amphotericin B is reserved for esophageal candidiasis during pregnancy and in patients with drug-resistant candidiasis.

OPC is a local infection. Risk factors include radiation, chemotherapy, antibiotics, and corticosteroids. Treatment is with local agents such as nystatin or clotrimazole.

Prophylaxis

Patients at risk of developing OPC may be given antifungal prophylaxis with topical antifungals, such as clotrimazole or miconazole.[4]

Viral Infections

Viral infections of the esophagus are caused by herpes simplex virus (HSV), cytomegalovirus (CMV), and uncommonly by, varicella-zoster virus (VZV). Diagnosis can be established by endoscopic biopsy.[3,12] In advanced stages, all 3 viruses may cause small mucosal ulcerations. Biopsies taken from the edge of an HSV-related ulcer show intranuclear inclusions and multinucleated giant cells. Inclusions can also be detected by immunohistochemistry, using monoclonal antibodies to HSV. Biopsies of CMV lesions show intranuclear inclusions in fibroblasts and endothelial cells.

For patients with HSV esophagitis, acyclovir (400 mg orally 5 times daily for 14–21 days or 5 mg/kg intravenously every 8 hours for 7–14 days) is the therapeutic agent of choice. Acyclovir resistance in HSV results from mutations in the thymidine kinase (TK) gene of HSV.[13] Viruses with TK mutations are generally cross-resistant to valacyclovir but remain susceptible to drugs that act directly on DNA polymerase, such as foscarnet.[14] Cases of severe persistent infection with acyclovir-resistant HSV occur almost exclusively in immunocompromised patients. Famciclovir or valacyclovir can be considered in patients able to tolerate oral therapy, although there is limited clinical experience with these drugs in the treatment of HSV-associated esophagitis.

VZV esophagitis is initially treated with intravenous acyclovir because these patients usually have disseminated infection. After clinical improvement, treatment may be changed to an oral agent as used for HSV esophagitis.

CMV esophagitis is treated with intravenous ganciclovir (5 mg/kg twice daily) or foscarnet sodium (90 mg/kg twice daily) for 3 to 6 weeks.[15,16] The role of maintenance treatment after the clearance of infection is not well defined. Valganciclovir is an oral precursor of ganciclovir. Although valganciclovir has been approved for treatment of CMV retinitis in patients with AIDS and is used for prophylaxis against CMV infection in solid-organ transplant recipients, its role in CMV GI disease has not been studied. At a dose of 900 mg daily, valganciclovir produces systemic drug exposure equivalent to 5 mg/kg of intravenous ganciclovir.[15]

Bacterial Infections

Bacterial esophagitis can occur in immunocompromised patients and is usually polymicrobial, derived from oral flora.[3] Diagnosis is made by endoscopic biopsies that demonstrate the presence of bacterial clusters mixed with necrotic epithelial cells. Treatment with broad-spectrum antibiotics is usually successful.

Radiation-Induced Esophagitis

Radiation-induced esophagitis can occur during external beam radiotherapy of lung, head and neck, and esophageal cancers. Acute radiation esophagitis is primarily

caused by injury to the rapidly dividing cells of the basal epithelial layer, with subsequent thinning and denudation of esophageal mucosa. The severity of esophagitis depends on radiation dose and is exacerbated by concurrent use of chemotherapeutic agents such as cisplatin. Patients complain of odynophagia, dysphagia, and chest pain. Endoscopic findings include erythema, edema friable mucosa, ulcerations, or strictures.

Treatment includes use of local anesthetics such as viscous lidocaine hydrochloride and systemic narcotic analgesics and acid suppression with proton pump inhibitors and H_2 receptor antagonists. Esophageal strictures are treated by endoscopic dilation and refractory strictures may require placement of plastic stents. In patients with tracheoesophageal fistula due to esophageal cancer, self-expanding metal or plastic stents are the treatment of choice and they can achieve fistula closure in 70% to 100% of patients.[17]

DIARRHEA

Diarrhea is associated with several chemotherapeutic agents, particularly fluoropyrimidines such as 5-fluorouracil (5-FU) and capecitabine; irinotecan; and abdominal or pelvic radiotherapy. Other causes include small-molecule therapy, monoclonal antibodies, neutropenic enterocolitis, and *Clostridium difficile* infection (CDI).

Chemotherapy-Induced Diarrhea

Both 5-FU and irinotecan cause acute damage to intestinal mucosal epithelium leading to clinically significant diarrhea.[18] The severity of chemotherapy-induced diarrhea is determined by the frequency and volume of stool output. Diarrhea is reported in up to 50% of patients receiving weekly 5-FU/leucovorin combined treatment. It tends to be worse in patients receiving irinotecan hydrochloride, 5-FU, and leucovorin than in those receiving 5-FU and leucovorin without irinotecan.[19] Other factors that can increase the risk of 5-FU–induced diarrhea include female sex, the presence of an unresected primary tumor, and previous chemotherapy-induced diarrhea.[20]

Irinotecan can cause early-onset diarrhea, which is mediated via cholinergic receptors, and can be effectively treated with atropine and loperamide hydrochloride. In contrast, late-onset diarrhea associated with irinotecan hydrochloride is unpredictable and occurs at all doses. It is seen less frequently when irinotecan is given every 3 weeks rather than weekly. Diarrhea also occurs frequently with regimens that combine 5-FU, leucovorin, and oxaliplatin.[21]

Diarrhea commonly occurs in patients receiving small-molecule epidermal growth factor receptor–tyrosine kinase inhibitors. Grade 1 to 2 diarrhea, as defined by the National Cancer Institute's common toxicity criteria, has been reported in up to 56% of patients receiving erlotinib.[22] Another small-molecule inhibitor, sorafenib, is associated with diarrhea in approximately 34% of patients.[23]

Radiation-Induced Diarrhea

Radiotherapy causes injury to the GI mucosa. Pelvic or abdominal radiotherapy can lead to acute enteritis, characterized by abdominal cramping and diarrhea in approximately 50% of patients. These symptoms are made worse by concomitant chemotherapy.[24] Symptoms typically occur during the third week of fractionated radiotherapy.

Treatment of Chemotherapy- and Radiation-Induced Diarrhea

In 1998, Wadler and colleagues[25] published guidelines on the treatment of chemotherapy-induced diarrhea. These guidelines were revised by an expert panel in

2004.[26] The panel stressed the need for close monitoring of patients receiving a combination of irinotecan, 5-FU, and leucovorin and other intensive combination regimens, including weekly assessment of GI toxicity, particularly for older patients.

Opioid agonists are the cornerstone of therapy for chemotherapy-induced diarrhea. Loperamide and diphenoxylate are both widely used and are approved by the US Food and Drug Administration (FDA) for this indication; loperamide is more effective. For mild to moderate diarrhea, an initial dose of 4 mg of loperamide hydrochloride may be given, followed by a further 2-mg dose every 4 hours or after every stool discharge. Severe diarrhea often requires a more aggressive regimen, with an initial dose of 4 mg of loperamide hydrochloride followed by a further 2-mg dose every 2 hours or 4-mg dose every 4 hours until the patient is diarrhea-free for 12 hours.[26,27]

This high-dose loperamide has been used effectively for the control of irinotecan-induced diarrhea. Octreotide, a synthetic long-acting somatostatin analogue, has been used as a second line therapeutic agent in opioid-resistant patients. It decreases the secretion of vasoactive intestinal peptide, prolongs intestinal transit time, and reduces secretion of intestinal fluid and electrolytes. The recommended initial dose of octreotide is 100 to 150 mcg given subcutaneously 3 times daily or 25 to 50 mcg/h every hour if given as an intravenous infusion. Sucralfate, a nonsystemic aluminum hydroxide complex, has been studied for control of radiotherapy-induced diarrhea and mucosal injury, with only limited, if any, benefit. In fact, sucralfate may aggravate GI symptoms such as rectal bleeding.[28]

Other drugs used as adjunctive therapeutic agents in chemotherapy- or radiation-induced diarrhea include absorbents such as kaolin and charcoal, deodorized tincture of opium, paregoric, and codeine phosphate. **Fig. 1** shows an algorithm for the management of chemotherapy-induced diarrhea.

Optimal dose of octreotide

Octreotide can be titrated to higher doses (500–2500 mcg 3 times daily) for the treatment of those who do not respond to lower doses.[29] Early studies of octreotide for chemotherapy-induced diarrhea investigated subcutaneous doses ranging from 50 to 100 μg twice or thrice daily.[26] Recent data suggest that higher doses may be more effective. Goumas and colleagues[30] compared 100-μg octreotide with 500 μg administered 3 times a day in 59 patients with grade 3 or higher grade of chemotherapy-induced diarrhea who failed to respond to loperamide (4 mg 3 times a day) for at least 48 hours. Treatment with 500-μg octreotide was significantly more effective than with 100 μg (90% vs 61% of patients had complete resolution of diarrhea; $P<.05$), and both doses were well tolerated, suggesting that 500-μg octreotide given 3 times a day may be more effective than lower doses in patients who fail to respond to loperamide.

Role of prophylactic antidiarrheal therapy

Because of the well-recognized risk of diarrhea associated with irinotecan, recent studies have investigated prophylactic regimens for chemotherapy-induced diarrhea. Long-acting slow-release formulations of octreotide long acting release (octreotide LAR) can be administered by an intramuscular injection once a month. Once steady state has been achieved, administration of a 20-mg intramuscular dose of octreotide LAR every 4 weeks produces the same pharmacologic effects as 150-μg octreotide given thrice a day by subcutaneous injection[31] and dramatically reduces fluctuations in peak and trough octreotide concentrations. Octreotide LAR, at a starting dose of 20 mg, effectively controls diarrhea associated with carcinoid syndrome,[31] and monthly doses of 20 to 30 mg of octreotide LAR are currently being investigated for the treatment and prevention of chemotherapy-induced diarrhea.

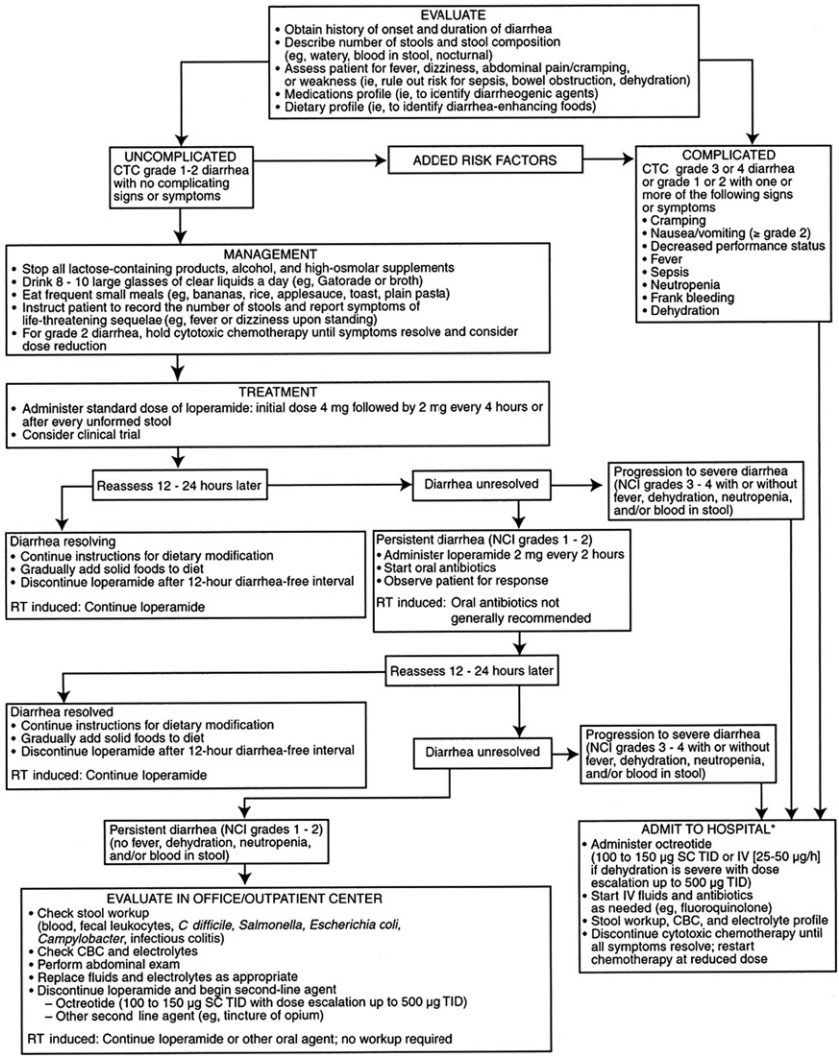

Fig. 1. Assessment and management of diarrhea complicating chemotherapy. Abbreviations: CBC, complete blood count; CTC, common toxicity criteria; IV, intravenous; NCI, National Cancer Institute; RT, radiotherapy; SC, subcutaneous. (*From* Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 2004;22:2918–26; with permission.)

Stem Cell Transplantation–Associated Diarrhea

Patients undergoing stem cell transplantation (SCT) can suffer from diarrhea caused by the conditioning regimen consisting of high-dose chemotherapy or radiotherapy, GVHD of the GI tract, or infection related to immunosuppressive therapy. Pretransplant conditioning regimens (including total body irradiation and/or combination chemotherapy) can injure the intestinal mucosa, as discussed earlier, causing secretory diarrhea that resolves after mucosal restitution. Transplant recipients of allogeneic

stem cells can also develop GI GVHD, which usually starts 3 weeks or later after transplant, after engraftment of donor hematopoietic stem cells. GVHD and its associated diarrhea are discussed in a separate section later.

CDI

CDI is the most common nosocomial infection of the GI tract.[32,33] Risk factors for CDI include a history of antibiotic therapy, bowel surgery, an immunocompromised state, and any process that suppresses the normal GI flora, including chemotherapy. CDI can occur up to 8 weeks after the end of a course of antibiotics, but patients undergoing cancer chemotherapy are predisposed to *C difficile*-induced diarrhea even in the absence of antibiotic therapy.[34] Clinical presentation of CDI can vary from mild diarrhea to pseudomembranous colitis with or without protein-losing enteropathy to fulminant colitis with toxic megacolon.

A diagnosis is established by detecting *C difficile* toxin in stool or by identifying pseudomembranous colitis on endoscopic examination. Rapid enzyme immunoassays for detecting toxin A or B or both are now commonly used. Endoscopically, pseudomembranes can be seen as adherent yellow plaques that vary in diameter from 2 to 10 mm (**Fig. 2**).[32] The rectum and sigmoid colon are typically involved, but in approximately 10% of cases, colitis is only present in the more proximal colon and can be missed during sigmoidoscopy.

Standard therapy for *C difficile*-associated diarrhea is with oral metronidazole or oral vancomycin. Metronidazole at a dose of 500 mg 3 times daily or 250 mg 4 times a day given either orally or intravenously for 10 to 14 days is as effective as oral vancomycin given at a dose of 125 mg 4 times daily.[35] The lower dose of vancomycin, 125 mg 4 times a day, is as effective as the higher dose, 250 mg 4 times a day, in case of mild to moderate diarrhea and is much less expensive.

Metronidazole has some advantages over vancomycin including lower cost and the observation that it can reduce selection of vancomycin-resistant enterococci. Metronidazole is, therefore, the initial therapy of choice in nonsevere cases of *C difficile*-induced diarrhea. If there is no improvement in 3 days, treatment with vancomycin should be initiated.

In patients with severe CDI and signs of systemic toxicity, the recommended treatment is vancomycin 125 mg orally 4 times daily, with dose escalation at 48-hour intervals up to 500 mg 4 times daily if patients fail to improve. If patients do not respond to

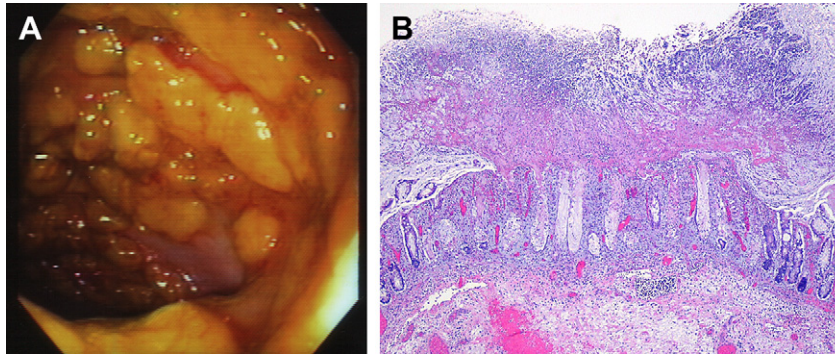

Fig. 2. Pseudomembranous colitis. (*A*) Plaquelike pseudomembranes adherent to the colonic mucosa observed endoscopically. (*B*) Typical lesion with luminal inflammatory exudates (hematoxylin-eosin).

oral vancomycin, the addition of intravenous metronidazole 500 mg every 8 hours or vancomycin retention enemas (0.5–1 g vancomycin dissolved in 1–2 L of normal saline every 4–12 hours) should be considered.[36]

The use of antidiarrheal agents is not recommended because the decreased transit time can lead to complications and lengthen the duration of illness.

Relapse of CDI is common, occurring in up to 10% to 25% of all patients with CDI. Relapses usually occur within 1 to 3 weeks after ending initial therapy and are probably caused by failure to eradicate the organism rather than by antibiotic resistance.[32] These patients are likely to relapse repeatedly. First relapses should be treated with a second 10- to 14-day course of oral metronidazole or vancomycin. If a patient relapses after taking a second course of antibiotics, different approaches have been suggested including tapered or pulsed antibiotic therapy, longer duration of treatment (several weeks), and the use of toxin-binding resins such as cholestyramine or colestipol hydrochloride alone or in combination with vancomycin.[37] In a small series, 2 weeks of vancomycin administration followed by 2 weeks of rifaximin administration has proved successful in controlling recurrent disease.[38] A recent study used 2 neutralizing human monoclonal antibodies against *C difficile* toxins A and B (CDA1 and CDB1, respectively) in 101 symptomatic patients, who were receiving either metronidazole or vancomycin. The rate of recurrence was significantly lower among patients treated with the monoclonal antibodies.[39]

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis is characterized by fever and right lower quadrant pain in neutropenic patients. It is seen in children and adults with hematologic malignancies, with aplastic anemia, and after myelosuppressive therapy for solid malignancies.[40] In a systematic review of 145 published articles, a 5.3% pooled incidence was reported in adults hospitalized for the treatment of hematologic malignancies, aplastic anemia, or solid tumors.[33]

Histologic examination of biopsy samples from patients with neutropenic enterocolitis is characterized by a thickened bowel wall, edema, mucosal ulcerations, focal hemorrhage, and mucosal or transmural necrosis. Numerous bacterial and/or fungal species have been identified in surgical specimens and peritoneal fluid from patients with neutropenic enterocolitis.[41] The diagnosis is usually established by computed tomography, when findings include a fluid-filled and dilated cecum, a right lower quadrant inflammatory mass, and pericecal fluid or inflammatory changes in the pericecal soft tissues.[41]

Treatment consists of bowel rest, intravenous fluids and broad-spectrum antibiotics. Cytopenia and coagulopathy associated with oncologic treatment should be treated, because neutropenia contributes to the pathogenesis of the disease and coagulopathy can be associated with blood loss from mucosal hemorrhage. Recombinant granulocyte colony-stimulating factor may hasten leukocyte recovery, which contributes to the resolution of neutropenic enterocolitis.[42] Surgery has been recommended for patients with persistent GI bleeding, despite treatment of cytopenia and coagulopathy, and for patients with perforation or clinical deterioration, despite pharmacologic therapy.[43]

GVHD

GVHD is classified as either acute or chronic based on the time of disease onset after allogeneic SCT. Acute GVHD generally occurs within the first 100 days of SCT, whereas chronic GVHD generally occurs more than 100 days after allogeneic SCT.

This classification is somewhat arbitrary because a continuum of clinical findings can be observed in patients with acute or chronic GVHD. Acute GVHD results from donor T lymphocytes recognizing and mounting an immune response against minor antigens present on the recipient cells.

Acute GVHD

The incidence of acute GVHD varies from 10% to 50% in patients undergoing allogeneic SCT from an HLA antigen–identical sibling or unrelated donor. The most common sites of involvement include skin, GI tract, and liver. Involvement of the GI tract is characterized by profuse watery diarrhea and abdominal cramping. The diarrhea can frequently become bloody.[44] Less commonly, patients may also present with upper GI symptoms, such as nausea, vomiting, and anorexia. Factors that increase the risk of developing GVHD include histoincompatibility, advanced age of the donor and/or recipient, sex mismatch, the use of peripheral stem cells rather than bone marrow stem cells, greater intensity of the conditioning regimen, and suboptimal prophylactic therapy with immunosuppressants.

The most consistent histologic feature of acute GVHD is the presence of apoptotic bodies,[45] although this feature is not specific to acute GVHD.

Use of methylprednisolone, 2 mg/kg, is the first line treatment of acute GVHD. Complete response can be seen in about 50% of patients. Those not responding to this dose by 5 days improve with higher dose of steroids (10 mg/kg). A durable response from steroid therapy occurs in only 25% to 40% of patients. Oral beclomethasone with prednisone may show a better response in treating GI GVHD. Steroid-refractory acute GVHD is usually defined as progression of GVHD in the first 72 hours of steroid therapy or a lack of improvement after 3 to 7 days of steroid therapy.

Steroid-refractory patients may require additional immunosuppressive agents, including mycophenolate mofetil, antithymocyte globulin (ATG; Thymoglobulin), or infliximab. ATG has been commonly used as an initial salvage therapy in steroid-refractory acute GVHD, even though its effect on patient survival is limited. McCaul and colleagues[46] studied ATG in patients with steroid-refractory acute GVHD. Antithymocyte globulin, 2.5 mg/kg/d, was given intravenously for 4 to 6 days or on days 1, 3, 5, and 7. Of 36 patients, 2 withdrew from the study due to adverse reactions (hypoxemia and hypotension) and 34 were evaluated. Response rates were highest in patients with skin involvement (96%) and lowest in those with liver involvement (36%). The most common adverse events were infections (82%), leucopenia (25%), hepatic dysfunction (25%), posttransplant lymphoproliferative disease, and infusion-related reactions (19%). Only 2 patients (6%) were alive at 15 months. Cyclophosphamide is an alkylating agent that exhibits potent immunosuppressant activities and is effective in acute GVHD of the skin and liver, but response to cyclophosphamide has been poor in those with advanced GI tract involvement. Mycophenolate mofetil is a fungus-derived antibiotic that exhibits immunosuppressant activities. A 60% response rate to mycophenolate therapy is reported in patients with acute GVHD. Infliximab is a chimeric monoclonal antibody that binds to tumor necrosis factor α (TNF-α), thereby interfering with endogenous TNF-α activity. A multicenter retrospective study evaluated the efficacy of infliximab in patients with steroid-refractory acute GVHD.[47] The overall response rate was 59%, with a favorable outcome in younger (<35 years) male patients with GI involvement.

Chronic GVHD

Chronic GVHD is seen in up to 50% of patients after sibling or unrelated-donor SCT, generally occurring more than 100 days after transplantation.[48] The pathogenesis of

chronic GVHD involves immunodysregulation, resulting from both autoimmune and alloimmune reactions. It may only affect skin or mucosal surface (mucocutaneous chronic GVHD) or visceral organs, such as liver or lungs. Chronic GI GVHD primarily affects the upper GI tract and may present as dry mouth or oral ulcers. Esophageal involvement may lead to formation of painful esophageal ulcers, webs, rings, and strictures. The small bowel and colon are less frequently involved. Patients present with diarrhea, malabsorption, submucosal fibrosis, and sclerosis of the intestine.[49]

The liver is commonly involved in acute and chronic GVHD. Pathologic examination reveals extensive bile duct damage with bile duct atypia and degeneration, epithelial cell dropout, and lymphocytic infiltration of small bile ducts leading to cholestasis.[50]

Initial therapy for chronic GVHD includes administration of corticosteroids at a dose of 1 mg/kg/d unless contraindicated by a comorbid disease. Infection is the primary cause of death. Patient education, infection prophylaxis, and supportive care are important components of chronic GVHD management.[51] Symptomatic relief rather than resolution of chronic GVHD can provide great benefits by improving patients' functional status and quality of life.

RADIATION PROCTITIS

Patients receiving radiation for the treatment of gynecologic, genitourinary, GI, and other malignancies are at risk of developing acute or chronic intestinal injury. Acute radiation injury in the rectum and distal colon usually occurs within 6 weeks of therapy and is characterized by diarrhea, rectal urgency, tenesmus, and, occasionally, rectal bleeding. These symptoms usually resolve within 6 months without the need for therapy.[52]

Chronic radiation proctitis or coloproctitis has a delayed onset, occurring approximately 1 year or later after exposure to radiation. It is caused by obliterative endarteritis and chronic mucosal ischemia, resulting in epithelial atrophy and fibrosis. It may end in stricture formation and bleeding within the colon and rectum. Patients with radiation proctitis often present with diarrhea, bleeding, tenesmus, urgency, difficulties with defecation, and less commonly, fecal incontinence.

The diagnosis of radiation proctitis is made by colonoscopy or sigmoidoscopy when mucosal edema, erythema, friability, and telangiectasias may be seen. In severe cases, mucosal ulcerations and strictures can be observed.[28]

Treatment of radiation proctitis depends on symptoms. Sucralfate is largely ineffective and according to some studies, may increase the risk of rectal bleeding.[28] Other treatments that have shown some benefit in small clinical trials include hyperbaric oxygen[53] and short-chain fatty acid enemas.[54]

Various thermal endoscopic interventions have also been used successfully to treat bleeding associated with radiation proctitis, including argon plasma coagulation, argon and Nd:YAG lasers, bipolar electrocoagulation, and heater probes.[55,56] Surgery should be considered in patients with intractable symptoms such as strictures, pain, or bleeding.[57] The selection of treatment of radiation proctitis should be based on the type and severity of symptoms as well as local expertise.

CONSTIPATION

Constipation is a common problem in patients undergoing cancer treatment and is usually caused by a combination of poor oral intake, decreased physical activity, and drugs such as opioid analgesics or antiemetic agents including ondansetron. These agents slow intestinal transit time. Constipation has also been reported in patients taking vinca alkaloids, in particular vincristine and thalidomide.[58]

Impaction, bowel obstruction, and colonic pseudo-obstruction must be ruled out before starting therapy for constipation, which should be anticipated in the patient with cancer, and general steps should be taken to avoid this complication. Electrolyte abnormalities and other reversible causes of constipation should be treated. Drugs that cause constipation should be discontinued if possible. Laxatives, with or without stool softeners, can be used initially, including stimulant laxatives, such as bisacodyl and senna, which alter electrolyte transport by the intestinal mucosa and increase intestinal motor activity. If these laxatives are not effective, osmotic agents such as lactulose or sorbitol can be effective at improving stool frequency and consistency. Polyethylene glycol solutions are available in powder form and improve chronic constipation. Drugs to improve colonic transit have been disappointing. Metoclopramide is ineffective, and tegaserod (a 5-hydroxytryptamine receptor agonist) has significant cardiovascular adverse effects. Tegaserod is still available in the United States under an emergency investigational new drug protocol from the FDA. It is contraindicated in women older than 55 years and has not been studied well in men and therefore, its availability and clinical application are limited.

Lubiprostone, a chloride channel activator, is FDA approved for the treatment of chronic idiopathic constipation. It is a bicyclic acid that works locally on the apical aspect of the intestinal epithelial cell and increases fluid secretion and intestinal motility. It may be useful in patients with opioid- and chemotherapy-induced constipation.

In April 2008, the US FDA granted approval to methylnaltrexone, the first peripheral micro-opioid–receptor antagonist for the treatment of opioid-induced constipation in advanced-illness patients. Methylnaltrexone, a derivative of naltrexone, selectively antagonizes the peripheral microreceptors in the GI tract without central effects. Subcutaneous methylnaltrexone reversed opioid-induced constipation after the first dose in approximately 50% to 60% of the patients.[59] In most of the cases, the benefit was seen within an hour. Methylnaltrexone does not affect opioid analgesic effects or induce opioid symptoms.

DRUG-INDUCED HEPATOTOXICITY

Patients undergoing chemotherapy require careful assessment of liver function both before and during therapy. If liver function test results are abnormal, the cause must be defined promptly. In addition to drug reactions, there are multiple possible causes of abnormal liver function test results in patients undergoing chemotherapy, including tumor progression, infection, or the presence of coexisting hepatic disease.

Hepatitis

Patients with a preexisting liver disease can be more susceptible to drug-induced hepatotoxicity. Chemotherapy (including the use of monoclonal antibodies) can reactivate hepatitis B virus (HBV) and associated diseases,[60,61] and risk factors include HBV surface antigen and HBV envelope antigen seropositivity, detectable HBV DNA before chemotherapy, male sex, diagnosis of lymphoma or breast cancer, and use of steroids.[62,63]

Prophylactic treatment with lamivudine seems to be beneficial in preventing HBV reactivation or reducing the severity of HBV-related diseases in patients on cytotoxic chemotherapy.[64] For short-term prophylaxis (<6 months), lamivudine is a reasonable choice because the risk of lamivudine resistance is extremely low. If treatment is required for more than 6 months, the use of either adefovir dipivoxil or entecavir instead of lamivudine is recommended.[65]

The relationship between chemotherapy and hepatitis C virus (HCV) reactivation is less clear. It seems that HCV infection increases the risk of abnormal liver function tests[66]; however, severe flares of clinical hepatitis are extremely rare.

Idiosyncratic Hepatotoxicities

Most hepatotoxic drug reactions are idiosyncratic and caused by hypersensitivity mechanisms or host metabolic idiosyncrasy.[67] Treatment is largely supportive by monitoring liver function and discontinuation of the drug.

Alkylating agents

Alkylating agents are not commonly associated with hepatotoxicity, and with the exception of cyclophosphamide and ifosfamide, patients receiving alkylating agents generally do not require any dose reduction. Cyclophosphamide is rarely hepatotoxic, probably due to an idiosyncratic reaction, if it occurs. On rare occasions, diffuse hepatocellular destruction and massive hepatic necrosis have been described with cyclophosphamide.[68] Other alkylating agents, including melphalan, chlorambucil, nitrogen mustards, and busulfan, do not depend on the liver for metabolism and are not frequently associated with hepatotoxicity.

Antimetabolites

The antimetabolites include cytarabine, 5-FU, 6-mercaptopurine (6-MP), azathioprine, 6-thioguanine, and methotrexate. Hepatic metabolism is important in the processing of these drugs, and dose reductions are usually necessary in patients developing liver dysfunction.

Cytarabine is used for the treatment of acute myelogenous leukemia and has rarely been associated with cholestasis, which seems reversible. There are rare reports of hepatotoxicity with intravenous 5-FU; however, hepatotoxicity is more common when 5-FU is administered in combination with ascaricides.[69] Intra-arterial administration of the 5-FU metabolite floxuridine (fluorodeoxyuridine) has been associated with 2 types of toxicity one is suggestive of hepatocellular injury and the other consistent with sclerosing cholangitis.[70] 6-MP is often used in the maintenance therapy for acute lymphoblastic leukemia, and 2 patterns of toxicity have been reported: hepatocellular injury and cholestasis. Hepatotoxicity caused by 6-MP occurs more commonly when a daily dose of 2 mg/kg is exceeded. Toxicity with azathioprine, a nitroimidazole derivative of 6-MP, is less common and less dose dependent than with 6-MP. High-dose methotrexate has been associated with reversible elevation in levels of aminotransferases.[71] Patients taking long-term low-dose methotrexate therapy are at risk of developing hepatic fibrosis and cirrhosis; however, the risk is low in patients who receive less than 1.5 g of methotrexate as a cumulative dose.

Antitumor antibiotics

The antitumor antibiotics, which include doxorubicin hydrochloride and daunorubicin, can cause hepatocellular injury and steatosis. With doxorubicin, dose reduction has been recommended in patients with cholestasis to avoid further toxicity.[72] Similar guidelines are recommended for daunorubicin.

Neoadjuvant regimens

Combinations of 5-FU and oxaliplatin or irinotecan hydrochloride are used as agents of neoadjuvant therapy in patients with colorectal cancer, before resection of liver metastases. These regimens have been associated with steatosis, hepatic vascular injury, and nodular regenerative hyperplasia.[73] Venoocclusive disease has also been

seen with many chemotherapeutic agents including dacarbazine, 6-MP,[74] cyclophosphamide, and busulfan.[75]

OTHER COMPLICATIONS

Nausea and Vomiting

Nausea and vomiting frequently occur after administration of chemotherapeutic agents. The likelihood of developing nausea and vomiting after chemotherapy depends on several factors including the dose and the intrinsic emetogenicity of a given agent.[76] The emetogenic potential of intravenously administered antineoplastic agents is assigned to 5 levels, ranging from minimal or less than 10% risk (eg, bevacizumab) to high or greater than 90% risk (eg, cisplatin). Emesis can be acute (occurring within the first 24 hours) or delayed.

Various antiemetic agents are now available for the prevention and treatment of chemotherapy-induced nausea and vomiting. These agents include drugs with a high therapeutic index such as 5-hydroxytryptamine 3 receptor antagonists (eg, ondansetron, granisetron, dolasetron, tropisetron, palonosetron), neurokinin 1 receptor antagonists (eg, aprepitant), and corticosteroids (usually used in combination with other agents). Agents with a low therapeutic index are also used, such as metoclopramide hydrochloride, butyrophenones, phenothiazines, cannabinoids, and olanzapine. The preferred agent and regimen depend on the emetogenic level of a given chemotherapeutic drug. For drugs with a low emetogenic risk, antiemetics are given only before chemotherapy, whereas for drugs with a high emetogenic risk (level 3 or higher), antiemetics are provided before and after chemotherapy.

GI Perforation, Fistula Formation, Arterial Thrombosis, and Bleeding

GI perforation, fistula formation, arterial thrombosis, and bleeding have been reported with bevacizumab, a monoclonal antibody against vascular endothelial growth factor,[77] with perforation reported in 1% to 2% of patients treated for metastatic colorectal cancer.[78] Risk for perforation includes an intact primary tumor, prior irradiation, acute diverticulitis, intra-abdominal abscess, and GI obstruction.

Acute Pancreatitis

Acute pancreatitis in patients with cancer or in those who have undergone hematopoietic SCT can be caused by conditions present in the general population, including gallstones and alcohol consumption. However, other causes should be considered when managing patients with cancer with acute pancreatitis, including medications and chemotherapeutic agents.

Drug-induced pancreatitis has no distinguishing features, and therefore taking a careful drug history and excluding other causes are essential to diagnosis. Drugs known to cause acute pancreatitis include metronidazole, sulfonamides, tetracycline, furosemide, thiazides, estrogen, and tamoxifen.[79] During chemotherapy, pancreatitis has been reported with azathioprine, prednisone, cytosine arabinoside, and various regimens of combination chemotherapy, including vinca alkaloids, methotrexate, mitomycin, 5-FU, cyclophosphamide, cisplatin, and bleomycin.[80]

Oral Mucositis or Ulceration of the Oropharynx

Oral mucositis occurs frequently in patients undergoing radiotherapy and chemotherapy for solid malignancies and in up to 98% of those undergoing hematopoietic SCT.[81] Palifermin, a recombinant human keratinocyte growth factor, decreases the incidence and duration of mucositis in patients with hematologic malignancies, who are receiving chemotherapy and requiring the support of SCT. Use of palifermin is

approved by the FDA for this indication. Results from phase I and II trials in patients receiving chemotherapy for solid tumors are also encouraging.[81]

SUMMARY

Cancer therapy can frequently cause a host of adverse GI events. Chemotherapy and radiotherapy have increased in complexity, with greater therapeutic effectiveness achieved from combination therapies. These therapies often result in more severe complications, including esophagitis, diarrhea, and drug-induced hepatotoxicity, which reduce quality of life and can be life threatening. The immunocompromised state induced by oncologic therapy is also an important contributing factor underlying GI complications.

The gastroenterologist has an important role in managing the GI complications associated with various cancer treatments. A growing number of pharmacologic agents designed to address the pathophysiology of complications related to oncologic therapies are becoming available. These agents are leading to a mechanism-based approach to treating these often life-threatening situations.

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