Managing Toxicities Associated With Colorectal Cancer Chemotherapy and Targeted Therapy:
A New Guide for Nurses

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This article will provide an overview of the principal toxicities associated with commonly used chemotherapy treatment regimens for metastatic colorectal cancer (mCRC) and explore the role of the oncology nurse in the management of treatment-associated toxicity. Although patients with mCRC have benefited considerably from recent therapeutic advances, the use of more complex treatment regimens has inevitably resulted in an increase in treatment-related toxicities. This can ultimately lead to dose reductions, delays, or discontinuation of therapy, which may negatively affect efficacy outcomes. Early identification and treatment of toxicities often can allow treatment to continue as planned or at a lower dose, if required. The oncology nurse is ideally positioned to assist with the timely recognition and management of side effects. This allows therapy to be continued on schedule and at the appropriate dose, enabling patients to achieve a better clinical outcome and maintain or improve their quality of life.

Colorectal cancer is the third-most common cancer in both men and women in the United States, with about 150,000 new cases and 50,000 deaths estimated to have occurred in 2008 (Jemal et al., 2008). In addition, as many as 25% of patients have metastatic disease at the time of diagnosis (Sun & Haller, 2005). Several active drugs are now available to treat patients with metastatic colorectal cancer (mCRC), providing a choice of treatment options for first and subsequent lines of therapy. Current treatment standards provide a median overall survival of 20 months or more compared with 6–8 months for best supportive care (Goldberg et al., 2007). The addition of the new targeted agents to standard chemotherapy regimens can improve response rates and survival (Hwang & Marshall, 2006). In some studies, absolute response rates were about 10%–50% with the addition of these agents; response rates to most control regimens were 25% or lower (Borner et al., 2008; Giantonio et al., 2007; Hochster et al., 2008; Kabbinavar, Schulz, et al., 2005; Popov, Milicevic, & Radosevic-Jelic, 2008; Sobrero et al., 2008; Van Cutsem, Nowacki, et al., 2007; Van Cutsem, Peeters, et al., 2007).

Although patients with mCRC have benefited considerably from therapeutic advances, more complex regimens are predictably associated with increased toxicity (Grothey, 2006). This article provides an overview of the main toxicities associated with commonly used mCRC treatment regimens and explores the role of the oncology nurse as part of a multidisciplinary team managing treatment-associated toxicity.

At a Glance

- Advances in the treatment of metastatic colorectal cancer have given patients new hope of extended survival and improved response rate.
- Recommended combination regimens, which may include biologic agents as well as standard chemotherapy, have a variety of toxicities. Toxicity management is key to ensuring delivery of the planned dose and treatment schedule.
- Oncology nurses play a key role within the multidisciplinary team, acting as a liaison between the patient and the oncology team. Nurses are, therefore, in an ideal position to not only educate patients regarding the potential toxicities that may be encountered during treatment but also to identify and manage toxicities before they become problematic.

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Chemotherapy Options for Metastatic Colorectal Cancer

The U.S. Food and Drug Administration (FDA) has approved several active agents for the treatment of patients with mCRC. Traditional chemotherapeutic agents for mCRC include 5-fluorouracil (5-FU)/leucovorin, oxaliplatin, irinotecan, and capecitabine. Newer targeted agents, such as bevacizumab, cetuximab, and panitumumab, have been approved by the FDA and added to the standard treatment options for increased efficacy benefits (Cunningham et al., 2004; Giantonio et al., 2007; Hurwitz et al., 2005; Kabbinavar, Hambleton, et al., 2005; Kabbinavar, Schulz, et al., 2005). These drugs can be administered as single agents or combined in various regimens to offer patients the best possible outcomes.

Several issues must be considered when planning treatment. Whether this will be first-line therapy may impact the treatment options available, as will any prior treatments and the patient's ability to tolerate the potential side effects of chemotherapy. In patients who are able to tolerate intensive therapeutic regimens, first-line treatment is likely to consist of oxaliplatin or irinotecan combined with 5-FU or capecitabine plus bevacizumab (National Comprehensive Cancer Network [NCCN], 2007b). For patients receiving second-line treatment, cetuximab also may be included as it has been shown to extend disease-free survival in patients with irinotecan-refractory mCRC (Cunningham et al., 2004). Patients unable to tolerate intensive therapy usually are treated with a fluoropyrimidine—capecitabine or infusional 5-FU/leucovorin—in the first-line setting, either with or without bevacizumab. More intensive chemotherapy may be considered for patients who respond to initial treatment, although best supportive care may be more appropriate for patients who progress (NCCN, 2007b). Possible options for subsequent treatment also include participation in clinical studies.

Fluoropyrimidines

5-FU acts by inhibiting the thymidylate synthase enzyme, which is involved in pyrimidine nucleotide synthesis. 5-FU is usually administered with leucovorin, a reduced folate, which stabilizes the binding of 5-FU to thymidylate synthase and enhances the inhibition of DNA synthesis (Sobrero, Guglielmi, Grossi, Puglisi, & Aschele, 2000). In patients with advanced colorectal cancer, treatment with 5-FU/leucovorin extends median survival from approximately 6 months (without treatment) to about 11 months (Scheithauer, Rosen, Kornek, Sebesta, & Depisch, 1993; Thirion et al., 2004). The major side effects associated with 5-FU depend on the method and timing of administration. When 5-FU is given via IV according to a bolus schedule of five consecutive days' treatment every four to five weeks, neutropenia and stomatitis are the most common toxicities. Alternatively, when 5-FU is administered via IV according to a weekly bolus schedule (e.g., the Roswell Park regimen), diarrhea is more frequent (Buroker et al., 1994). Regimens involving 5-FU given as a continuous IV infusion are associated with fewer hematologic and gastrointestinal (GI) side effects, but palmar–plantar erythrodysesthesia, or hand–foot syndrome, is more common (Macdonald, 1999). Evidence suggests that this continuous infusion approach is somewhat more effective than the bolus regimens (de Gramont et al., 1997).

The newer agent capecitabine is a prodrug that undergoes enzymatic conversion to 5-FU within the body. The side effects of oral capecitabine are similar to those of 5-FU when given via IV, although a higher incidence of hand-foot syndrome and a lower incidence of stomatitis occur (Van Cutsem et al., 2001). Other side effects of capecitabine include diarrhea, nausea, and vomiting. Although less effective than combination regimens, monotherapy is generally associated with fewer adverse events (see Table 1) and may be appropriate for patients who are unable to tolerate intensive treatment. Grade 3 or 4 neutropenia has been reported in just 2.4% of patients receiving 5-FU/leucovorin delivered by continuous infusion (Douillard et al., 2000) compared with rates of up to 59% in patients receiving combination regimens. However, grade 3 or 4 diarrhea is more common with 5-FU/leucovorin continuous infusion (21%–26% of patients) (Douillard et al.; Köhne et al., 2005) than with most combination regimens.

Oxaliplatin-Based Regimens

Oxaliplatin is widely used in the treatment of mCRC, usually in combination with other chemotherapy drugs. Commonly used regimens include FOLFOX (leucovorin, 5-FU, and oxaliplatin) and CapeOx (capecitabine and oxaliplatin). Different versions of the FOLFOX regimen may be used, including FOLFOX4 (two-day cycles of 5-FU/leucovorin with oxaliplatin) and FOLFOX6 (high-dose intensity oxaliplatin combined with 5-FU/leucovorin every two weeks). Phase III studies of oxaliplatin in combination with 5-FU have demonstrated high response rates of 34%–54% and median overall survival durations of 15–21.5 months in advanced disease. The 21.5-month median

Table 1. Treatment Options for Patients With Colorectal Cancer: Grade 3 or 4 Toxicities in Phase III Clinical Trials

REGIMEN	DIARRHEA (%)	NEUROSENSORY (%)	NEUTROPENIA (%)	OTHER (%)
Capecitabine	11–15	–	–	HFS, 16–18
CapeOx	13–15	11–25	5–7	HFS, 2–10
5-FU/LV (infusional)	21–26	–	2–5	–
FOLFIRI	10–14	–	10–28	–
FOLFOX4	5–12	4–18	10–59	–
IFL	23–29	–	40–54	–
mFOLFOX6	7–11	25–34	44–47	–
rIFL	16	–	27	–

CapeOx—capecitabine and oxaliplatin; 5-FU—5-fluorouracil; FOLFIRI—infusional 5-FU and irinotecan; FOLFOX—5-FU and oxaliplatin; HFS—hand-foot syndrome; IFL— irinotecan and bolus 5-FU; LV—leucovorin; mFOLFOX—modified FOLFOX; rIFL—reduced-dose irinotecan and 5-FU

overall survival reported for FOLFOX6 in a study by Tournigand et al. (2004) is one of the highest reported in patients with mCRC.

The most commonly observed toxicities in patients treated with FOLFOX4 and FOLFOX6 are neutropenia, neurologic toxicity, and diarrhea. Grade 3 neurotoxicity has been reported in 4%–18% of patients treated with FOLFOX4 (de Gramont et al., 2000; Goldberg et al., 2004, 2006) and in 25%–34% of patients treated with FOLFOX6 (Ducreux et al., 2007; Tournigand et al., 2004).

CapeOx has achieved response rates of 37%–48% and median overall survival times of 16.8–19.9 months in Phase III studies of patients with mCRC (Diaz-Rubio et al., 2007; Ducreux et al., 2007; Porschen et al., 2007). Hematologic toxicities are generally less common with CapeOx than with FOLFOX regimens. Capecitabine-associated grade 1 or 2 hand-foot syndrome has been reported in 14% of patients receiving CapeOx (Diaz-Rubio et al.), with grade 3 or 4 hand-foot syndrome in 2%–3% (Diaz-Rubio et al.; Ducreaux et al.).

Injection-site reactions following the administration of oxaliplatin have been reported, including inflammation, redness, and severe vein pain. Extravasation, including necrosis, also has been reported (sanofi-aventis, 2007).

Irinotecan-Based Regimens

The irinotecan-based treatment most commonly used in mCRC involves the combination known as FOLFIRI (folinic acid, 5-FU, and irinotecan). This regimen has been evaluated in several randomized phase III studies; response rates range from 31%–56% and median overall survival from 14–20.6 months (Colucci et al., 2005; Falcone et al., 2007; Souglakos et al., 2006; Tournigand et al., 2004). The once widely used IFL regimen (irinotecan with bolus 5-FU and leucovorin) is now considered to be inferior to FOLFIRI and FOLFOX (Goldberg et al., 2004, 2006).

Neutropenia and diarrhea are the principal toxicities associated with FOLFIRI and IFL. High levels of grade 3 or 4 neutropenia and diarrhea have been observed in patients treated with IFL (Goldberg et al., 2004), although the toxicities can be reduced by decreasing the doses of the component agents (Goldberg et al., 2006).

Biologic Agents

The addition of targeted agents to standard chemotherapy has the potential to significantly improve response rates and survival outcomes (Arnold, Siewczynski, & Schmoll, 2006; Cunningham et al., 2004; Giantonio et al., 2007; Hurwitz et al., 2004, 2005; Kabbinavar, Hambleton, et al., 2005, Kabbinavar, Schulz, et al., 2005; Saltz et al., 2007). Studies have demonstrated that the status of the *K-ras* gene in the tumor is predictive of outcomes with anti-epidermal growth factor receptor (EGFR) therapies. The presence of *K-ras* mutations within the tumor is associated with resistance to EGFR targeted therapy, and benefits of treatment with panitumumab and cetuximab appear to be limited to patients whose tumors contain wild-type (nonmutated) *K-ras* (Amado et al., 2008; Karapetis et al., 2008).

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that prevents the interaction of vascular endothelial growth factor with vascular endothelial cell receptors, thereby inhibiting angiogenesis (Franson & Lapka, 2005). Several randomized phase III studies have established the benefit of adding bevacizumab to standard chemotherapy regimens in patients with mCRC (Giantonio et al., 2007; Hochster et al., 2006; Hurwitz et al., 2004, 2005; Kabbinavar, Hambleton, et al., 2005, Kabbinavar, Schulz, et al., 2005). Common toxicities associated with bevacizumab treatment include hypertension, wound healing complications, proteinuria, and bleeding (commonly in the form of epistaxis). Nasal septum perforation has occasionally been associated with bevacizumab therapy (Roche Pharma AG, 2007a) and grade 3 or 4 hypertension has been reported in 6%–18% of patients receiving bevacizumab 5 mg/kg (Giantonio et al.; Hurwitz et al., 2004, 2005). Other potential side effects of bevacizumab include GI perforation, arterial thromboembolism and, rarely, posterior leukoencephalopathy syndrome (Roche Pharma AG, 2007a).

Cetuximab

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody that inhibits EGFR and prevents cell differentiation, proliferation, migration, and angiogenesis (Moosmann & Heinemann, 2007). In patients with irinotecan-refractory EGFR-expressing tumors, the combination of cetuximab with irinotecan was significantly more active than cetuximab alone (Cunningham et al., 2004). Common side effects associated with cetuximab treatment include cutaneous toxicity, hypersensitivity reactions (which may be severe), hypomagnesemia, and, rarely, pulmonary toxicity (Roche Pharma AG, 2007b). Data suggest that the occurrence of cetuximab-related hypersensitivity reactions may vary geographically in the United States. In O'Neil et al. (2007), 22% of patients treated with cetuximab in Tennessee and North Carolina experienced such reactions, compared with less than 1% in most centers in the northeastern United States. The variation appears to be related to the distribution of immunoglobulin E antibodies against galactose-α-1-3-galactose, which were found in 20.8% of control subjects in Tennessee, 6.1% from northern California, and 0.6% from Boston (Chung et al., 2008). Skin reactions (usually in the form of an acneiform follicular rash) occur in most patients receiving cetuximab (Yamamoto, Viale, & Zhao, 2004). Interestingly, survival duration appears to be improved in patients with a more pronounced cetuximab-associated skin rash (Van Cutsem, Nowacki, et al., 2007).

Panitumumab

Panitumumab is a human monoclonal antibody against EGFR. In the United States, panitumumab is approved as monotherapy in patients with mCRC who have failed treatment with a fluoropyrimidine plus either oxaliplatin or irinotecan. Skin-related toxicities, dermatitis, acneiform rash, erythema, and pruritus are the most common side effects of panitumumab and are experienced by about 90% of patients. Hypomagnesemia, diarrhea, and hypersensitivity reactions also may occur (Gibson, Ranganathan, & Grothey, 2006). About 15%–21% of patients experience hypersensitivity reactions to cetuximab (ImClone Systems Inc.,

2008). Such reactions are less common with panitumumab (about 2% of patients) (Amgen Inc, 2007b), perhaps because it is a fully human antibody.

Managing Toxicities

Although data show that the available treatments for patients with mCRC can have impressive survival benefits, anticipated side effects that need to be monitored and managed also exist. As well as affecting quality of life, side effects of treatment can lead to dose reductions, delays, and discontinuation, which may negatively affect efficacy outcomes. The early identification and management of toxicities can often allow treatment to continue as planned or at a lower dose. Evidence-based practice tools such as the Oncology Nursing Society (ONS) Putting Evidence into Practice (PEP) cards (ONS, 2008) provide nurses with easily accessible, up-to-date information on dealing with the major toxicities associated with cancer treatment. PEP cards review the interventions known to be used to treat major chemotherapy-associated toxicities and classify each approach according to the strength of evidence supporting it. Classifications range from "recommended for practice" through "effectiveness not established" to "not recommended for practice." Symptoms and management strategies for common treatment-associated toxicities are summarized in Tables 2 and 3.

Gastrointestinal Toxicity

Chemotherapeutic agents target the rapidly dividing cells of a tumor but also can affect other areas of the body where cells rapidly grow. The GI tract is lined with epithelial cells that have a high growth rate, making it vulnerable to the toxic effects of some chemotherapy drugs, including irinotecan (Alimonti et al., 2004) and 5-FU (Macdonald, 1999). Damage to these cells can result in adverse events such as anorexia, diarrhea, and nausea and vomiting.

Nausea and vomiting: An estimated 60% of patients who receive chemotherapy as part of their treatment experience some degree of nausea and vomiting (Bender et al. 2002). Several types of chemotherapy-induced nausea and vomiting (CINV) exist (Mitchell, 2006). Acute CINV occurs within 24 hours of drug administration and often within one hour. Delayed CINV occurs more than 24 hours after drug administration and often is a result of poor symptom control during the acute phase (Mitchell). Breakthrough CINV can occur even if symptoms are controlled and rescue medication is required. Occasionally, CINV is refractory to medication, and anticipatory nausea and vomiting can occur.

CINV generally results in altered nutritional and performance status and poor quality of life, which may affect patients' ability and desire to receive additional treatment. Prevention or effective treatment of CINV is, therefore, an important aspect

Table 2. Gastrointestinal, Neurologic, and Skin Toxicities: Symptoms, Characteristics, and Interventions

TOXICITY	CHARACTERISTICS	INTERVENTIONS
Acneiform rash	Macular or papular rash; itching; desquamation or lesions; macular, papular, or vesicular eruption; generalized ulcerative, exfoliative, or bulbous dermatitis (grade 4)	Topical agents with anti-inflammatory properties, antihistamine creams, topical moisturizers, tetracyclines, and treatment delay until symptoms resolve; grade 4 rash requires treatment in a specialized burn unit and treatment discontinuation
Acute neuropathy	Rapid onset; reversibility; transient paresthesia, dysesthesia, and hypoesthesia; numbness and tingling in the hands, feet, perioral area, or throat when exposed to cold; muscle cramping in hand or forearm; pharyngolaryngeal dysesthesia (dysphagia or dyspnea without stridor or wheezing)	Keeping warm and avoiding cold, prolonging oxaliplatin infusion time, occupational therapy, pain relief, education to prevent injury, dose reduction, reassurance, warming the body, and covering the mouth with a scarf to inhale warm air
Chronic neuropathy	Persistent, lasting more than 14 days; primarily peripheral and sensory; paresthesia, dysesthesia, and hypoesthesia; deficits in proprioception leading to difficulty writing, walking, swallowing, and buttoning clothes; can occur with no prior acute events	Reduction of oxaliplatin dose or discontinuation in cases of persistent grade 3 symptoms
Diarrhea	Dehydration, electrolyte imbalance, low immune function, malnutrition, inflammation, and abdominal pain	Dietary modification and adequate fluid intake; drug treatment with loperamide
Hand-foot syndrome	Numbness and sensitivity of the palms and soles, painful redness and swelling, desquamation, bullous swelling, and secondary infection; median time of onset is 79 days	Therapy interruption or discontinuation; avoidance of potential irritants, including tight clothes, changes in temperature, and excessive exercise; topical anesthetics and moisturizers
Mucositis	Burning sensation in mouth; inflammation, ulceration, discomfort, and pain; oral infection; inadequate oral intake; bloody diarrhea	Warm saline mouth rinses, cryotherapy, topical anesthetics, nutritional supplementation, and nystatin or fluconazole for candidiasis
Nausea and vomiting	Dehydration, electrolyte imbalance, weakness, and weight loss; acute syndromes appear within the first 24 hours of treatment; cumulative, delayed, refractory, and breakthrough syndromes also exist	Moderate emetic risk: premedication with dexamethasone, 5-HT_3 antagonist, and lorazepam on day 1; dexamethasone or 5-HT_3 antagonist on days 2–4. Low emetic risk: premedication with dexamethasone, or metoclopromide with or without lorazepam

5-HT_3— 5-hydroxytryptamine (serotonin)

Table 3. Hematologic Toxicities: Symptoms and Interventions

TOXICITY	SYMPTOMS	INTERVENTIONS
Anemia	Extreme tiredness, fatigue, dizziness, headache, tachycardia, inability to concentrate, pallor, and dyspnea	Blood transfusion as needed, erythropoietin therapy, and iron supplementation
Neutropenia	Sore throat; cough or dyspnea; nasal congestion; dysuria; redness; swelling, pain, and warmth at the site of an injury or at an IV or implanted catheter site; fever (febrile neutropenia)	Dose reduction or delay until blood count improves, antibiotics or antifungals for infection, and growth factors for febrile neutropenia
Thrombocytopenia	Excessive bruising, excessive bleeding, bleeding gums or epistaxis, petechiae, headache, hematuria or hematochezia, and serious internal bleeding	Dose reduction or delay, platelet transfusion as needed, and platelet growth factor oprelvekin for severe thrombocytopenia

of successful therapy. NCCN guidelines classify chemotherapy regimens according to their emetic potential and recommend treatment accordingly (NCCN, 2007a). An appraisal of pharmacologic and nonpharmacologic interventions for CINV also are available as a PEP card (Tipton et al., 2007). Agents used in the treatment of mCRC are classified for CINV as moderate risk (irinotecan and oxaliplatin), low risk (5-FU), and minimal risk (bevacizumab and cetuximab). Routine prophylaxis is not recommended for minimal-risk agents. For regimens that require administration of a moderately or highly emetic chemotherapy agent on several days of a treatment cycle, antiemetic treatment should include a serotonin (5-HT_3) antagonist with dexamethasone on each day of treatment. Owing to the potential side effects associated with antiemetic agents themselves (e.g., constipation, headaches), using the lowest possible effective antiemetic dose is desirable. Antiemetic regimens should be chosen based on the emetogenic potential of the chemotherapy regimen as well as patient-specific risk factors. Readers are referred to the NCCN guidelines for full details (NCCN 2007a). In Tipton et al., several pharmacologic agents (including benzodiazepines, 5-HT_3 receptor antagonists, corticosteroids, and neurokinin-1 receptor antagonists) are recommended for use on the basis of evidence from rigorously designed clinical studies. Other approaches, including acupuncture, acupressure, and progressive muscle relaxation, were classified as likely to be effective (Tipton et al.).

Diarrhea: Diarrhea can result from chemotherapy-induced cellular damage, which reduces absorption from the GI tract and increases the secretion of electrolytes into the stool. Severe diarrhea can cause hyponatremia, which can lead to seizures and coma and severe hypokalemia, which can impair cardiac function.

Irinotecan-induced diarrhea is categorized as early or late. Early occurs within the first 24 hours of irinotecan administration. Late occurs more than 24 hours after irinotecan administration and often is a serious, dose-limiting side effect (Hecht, 1998). The late and early diarrheas are thought to be related to increased cholinergic activity and the formation of an active metabolite, SN-38, respectively (Hecht). Diarrhea may be exacerbated by a deficiency of dihydropyrimidine dehydrogenase, an enzyme required to metabolize 5-FU, or by Gilbert syndrome, which is linked to an inability to metabolize irinotecan. Partial dihydropyrimidine dehydrogenase deficiency has an estimated frequency of about 3% (Milano & Etienne, 1994), and the incidence of Gilbert syndrome is 5%–10% in the U.S. (Hahn, Wolff, & Kolesar, 2006). In both cases, a wide variety of genetic variants exist and the influence that individual genotypes have on drug-associated diarrhea remains to be determined (Hahn et al.; van Kuilenburg et al., 2000). In patients known to be homozygous for one of the gene polymorphisms responsible for Gilbert syndrome, an initial reduced dose of irinotecan is recommended because the patient population is known to be at an increased risk of severe neutropenia. To date, genetic testing for dihydropyrimidine dehydrogenase deficiency or Gilbert syndrome is not part of routine clinical practice.

Careful attention to chemotherapy dosing and bowel function is necessary to avoid the development of severe diarrhea. Loperamide is standard therapy for uncomplicated mild to moderate chemotherapy-induced diarrhea and octreotide is recommended for severe diarrhea or diarrhea that is refractory to loperamide (Benson et al., 2004). Complicated cases require aggressive management, including antibiotics (Benson et al.). Other measures include dietary modification to avoid irritating the GI tract, reduced consumption of fiber, increased fluid intake, and replacement of lost salts.

Mucositis: Mucosal damage is a common side effect of 5-FU and is observed in many regions of the GI tract (Logan et al., 2009). Oral mucositis typically occurs 3–10 days after chemotherapy. It can make chewing and swallowing difficult, thereby interfering with nutrition. Speech also may be compromised. In addition, mouth sores are painful and susceptible to infection.

Treatment for mucositis is primarily palliative. A PEP card by Harris, Eilers, Harriman, Cashavelly, and Maxwell (2008) on the management of oral mucositis recommended the use of good oral care protocols (Eilers, 2004). For the clinician, the core elements of an oral care protocol include collaborating with a multidisciplinary team in all phases of treatment, conducting a systematic assessment at least daily, and providing instruction and education to the patient. Patients must undertake thorough tooth brushing and flossing; use mouthwashes; avoid tobacco, alcohol, and irritating foods; and maintain adequate hydration. Cryotherapy, involving oral cooling with ice chips or iced water, has been shown to be effective in preventing mucositis induced by 5-FU (Cascinu, Fedeli, Fedeli, & Catalano, 1994; Papadeas, Naxakis, Riga, & Kalofonos, 2007); this treatment is likely to be effective in the PEP classification (Harris et al.).

Palifermin, a synthetic growth factor that stimulates the growth of cells involved in protecting the lining of the mouth,

is approved by the FDA for use in patients with hematologic malignancies who require autologous stem cell transplantation (Spielberger et al., 2004). Although studies have shown palifermin to be effective in treating oral mucositis in patients with other cancers (Rosen et al., 2006), the agent is not currently approved for nonhematologic cancers. Harris et al. (2008) stated that, although palifermin is likely to be effective, its high cost means that it should only be used in patients likely to develop severe mucositis.

Neurotoxicity

Neurologic toxicities are commonly associated with the platinum analogs, including oxaliplatin (Grothey, 2005; Wickham, 2007; Wilkes, 2002). Oxaliplatin can cause two distinct types of neuropathy: acute self-limiting neuropathy and delayed cumulative sensory neuropathy. Acute neuropathy starts within one hour of oxaliplatin infusion and resolves within days to weeks. It may be associated with exposure to cold and affects about 90% of patients. Delayed neuropathy is cumulative and may increase in severity with each treatment cycle. In most cases, oxaliplatin-induced sensory neuropathy resolves after treatment is stopped. In a study by de Gramont et al. (2000), reversibility of grade 3 neurotoxicity was observed in 25 of 34 patients (74%), and the median time to recovery was 13 weeks. A predisposition may exist to neurotoxicity from antineoplastic agents in nerves already damaged by other conditions, including diabetes mellitus (Arne-Bes, 2004).

In a phase III study of FOLFOX4 in the treatment of patients with mCRC, the incidence of grade 3 neuropathy (defined as sensory loss or paresthesias interfering with function) reached 10% after 9 treatment cycles, 25% after 12 cycles, and 50% after 14 cycles. Grade 3 neuropathy resolved in 74% of patients after a median of 13 weeks (de Gramont et al., 2000).

Nurses play a key role in helping patients to understand the unusual neurologic toxicities associated with oxaliplatin therapy and can recommend approaches for alleviation, particularly simple coping strategies for sensory symptoms (Wilkes, 2002). Although no standard therapy exists for preventing or treating peripheral neuropathy, appropriate nursing care can play a key role in alleviating its symptoms. Reducing the dose of oxaliplatin for grade 2 neuropathy (sensory alteration that interferes with function but not with activities of daily living) can be effective in alleviating symptoms; however, discontinuation of oxaliplatin may be required in patients who experience grade 3 neuropathy (symptoms that interfere with activities of daily living) that persists between cycles. Nurses should perform a thorough review of subjective and objective assessments of the patient at baseline and with each cycle of treatment so that dose reductions are made before the onset of grade 3 neuropathy (Wilkes, 2007a, 2007b). "Stop and go" administration of oxaliplatin has been investigated as a strategy to help reduce neurotoxicity and enable patients to stay on treatment longer. A planned break from oxaliplatin (allowing any cumulative toxicity to resolve), followed by oxaliplatin reintroduction, appears to be feasible without loss of efficacy (de Gramont et al., 2007; Maindrault-Goebel et al., 2006; Tournigand et al., 2006).

To date, no prospective data are available on the prevention of peripheral neuropathy associated with oxaliplatin, although studies are ongoing with the investigational neurotrophic agent xaliproden (Wolfe, Barton, Kottschade, Grothey, & Loprinzi, 2008). Other agents that may ameliorate neuropathy symptoms include gabapentin and pregabalin, although the efficacy of these agents has not been conclusively proven in randomized clinical trials (Caraceni et al., 2004; Freynhagen, Strojek, Griesing, Whalen, & Balkenohl, 2005). Visovsky, Collins, Abbott, Aschenbrenner, and Hart (2007) reviewed studies employing various pharmacologic and nonpharmacologic interventions but concluded that none of the approaches was supported by sufficient evidence to enable their recommendation for practice.

Myelosuppression

Most chemotherapy regimens are associated with myelosuppression. Hematopoietic cells are, by nature, rapidly dividing and vulnerable to damage by chemotherapy. The clinical consequences of this damage can be life-threatening. Therefore, identifying and aggressively managing hematologic toxicities is imperative. Neutropenia is the most common hematologic toxicity associated with chemotherapy for mCRC and is a serious toxicity as a result of the risk of mortality from febrile neutropenia (Daniel & Crawford, 2006).

NCCN guidelines recommend prophylactic treatment with growth factors such as filgrastim, pegfilgrastim, and sargramostim for patients at high risk of developing febrile neutropenia, including patients who are undergoing treatment with anthracyclines or other high-risk agents, are being treated with more than two myelosuppressive agents, are expected to receive a planned dose intensity greater than 85% of standard, or experienced febrile neutropenia in a previous treatment cycle (NCCN 2007c). The use of growth factors in intermediate-risk patients is less clear-cut, and insufficient evidence exists for growth factor use in patients at low risk of febrile neutropenia.

Cutaneous or Integument Toxicity

Chemotherapy-related toxicities associated with the skin or integument include follicular rash and hand-foot syndrome. EGFR inhibition often is associated with an acneiform rash. Pharmacologic management of acneiform rash is determined by symptom severity (Thomas, 2005), and practical strategies that can be recommended to the patient include wearing loose-fitting cotton clothes, avoiding direct sunlight, and wearing sunscreen lotions, hats, and sunglasses when outdoors. Hydration of the skin can be assisted by using oil-based or oatmeal soap, using emollients after washing, and bathing instead of showering (Hetherington, Andrews, Vaynshteyn, & Fishel, 2007). Choice of treatment in individual cases depends on the severity of the rash, which is in turn dependent on several factors including patient age, skin color, and performance status. Proposals for the management of EGFR inhibitor-induced cutaneous toxicities recommend the use of topical and oral antibiotics (tetracycline, minocycline, trimethoprim-sulfamethoxazole, erythromycin), topical steroids, and anti-inflammatory preparations (Lynch et al., 2007). Overall, a proactive approach that includes measures to reduce the physical discomfort and severity of the side effects (using skin moisturizers and avoiding sunlight exposure) and a grade-based treatment algorithm is recommended (Oishi, 2008). Preemptive treatment with sunscreen, moisturizers, topical steroid, and doxycycline,

introduced 24 hours before the first dose, has been reported to reduce skin toxicities to panitumumab by about 50% (Lacouture et al., 2009). Finally, the appearance of an acneiform rash can have a severe psychological impact in some patients; therefore, as well as playing a key role in educating patients about the options for managing these side effects, oncology nurses should be prepared to offer appropriate emotional support in severely affected individuals (Yamamoto, Viale, & Zhao, 2004).

Hand-foot syndrome is commonly associated with 5-FU and capecitabine therapy. The precise mechanism underlying hand-foot syndrome remains unclear; however, the accumulation of drug metabolites in the skin probably is a factor (Lassere & Hoff, 2004). The management of hand-foot syndrome primarily involves treatment interruption or dose reduction and lifestyle changes (Gressett, Stanford, & Hardwicke, 2006; Marsé, Van Cutsem, Grothey, & Valverde, 2004; Roche Pharma AG, 2006). To date, insufficient evidence exists concerning the use of urea or amifostine to prevent hand-foot syndrome.

The management of other chemotherapy-associated skin and eye toxicities is beyond the scope of this review but has been reviewed by others (al-Tweigeri, Nabholtz, & Mackey, 1996; Segaert & Van Cutsem, 2005).

Cardiovascular Toxicity

Cardiovascular toxicities are most often associated with 5-FU-containing regimens (Alter, Herzum, Soufi, Schaefer, & Maisch, 2006; Jensen & Sorensen, 2006). Cardiotoxicity affects 1.2%–7.6% of patients receiving 5-FU and can lead to arrhythmias, myocardial infarction, and sudden cardiac death (Alter et al.). 5-FU toxicity usually is reversible, with resolution of acute complications such as arrhythmia. Prophylactic treatment with verapamil and nitrates should be considered for patients with coronary artery disease and in patients displaying symptoms following 5-FU treatment (Alter et al.).

Hypertension has been associated with bevacizumab, although the mechanism for this is not clearly understood (Giantonio et al., 2007). Symptomatic cardiovascular toxicity is rare, but serious events have been reported, including hypertensive crisis, cerebrovascular events, myocardial infarction, and reversible posterior leukoencephalopathy syndrome (Roche Pharma AG, 2007a). Blood pressure should be measured at the beginning of bevacizumab treatment, with regular monitoring thereafter. No specific recommendation exists for the frequency of blood pressure monitoring in patients receiving this agent. New-onset hypertension usually can be managed with standard antihypertensive medications such as β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, or diuretics (Gordon & Cunningham, 2005; Kozloff et al., 2007). Patients already receiving antihypertensive medication may require escalation of their existing antihypertensive regimen or the addition of another agent. If hypertension is not controllable with oral agents or if significant hypertension (above 150/100 mmHg) develops, bevacizumab should be stopped and, if a hypertensive crisis occurs, bevacizumab should be discontinued.

Hypersensitivity

Virtually all chemotherapy drugs have the potential to cause hypersensitivity reactions, which may affect any organ system and range in severity from mild pruritus to systemic anaphylaxis resulting in death (Zanotti & Markman, 2001). The prevention of hypersensitivity reactions should be a priority during chemotherapy, particularly with high-risk drug classes such as asparaginases, epipodophyllotoxins, taxanes, and platinum compounds. Protocols have been developed to help reduce the risk of chemotherapy-associated hypersensitivity reactions (Zanotti & Markman).

The symptoms of oxaliplatin-related hypersensitivity reactions are consistent with an IgE antibody-mediated reaction (Thomas, Quinn, Schuler, & Grem, 2003). Oxaliplatin-related hypersensitivity reactions have been reported to occur in 13%–19% of patients receiving the drug, although fatal anaphylactic reactions are rare (Brandi et al., 2003; Gowda, Goel, Berdzik, Leichman, & Javle, 2004; Siu, Chan, & Au, 2006; Thomas et al.). Most cases of oxaliplatin-associated hypersensitivity reactions occur after the patient has received multiple infusions of the drug. If a patient had a clinical benefit from chemotherapy before developing hypersensitivity reactions, it may be desirable to continue treatment. Patients who develop mild to moderate hypersensitivity reactions can be premedicated with corticosteroids and antihistamines and then rechallenged with oxaliplatin. Oxaliplatin should be discontinued in patients who develop more severe symptoms such as bronchospasm, cardiovascular collapse, and anaphylaxis. Prolonging the duration of the oxaliplatin infusion also may decrease the risk of hypersensitivity reactions (sanofi-aventis, 2007).

A trial period of desensitization may enable continuation of treatment after a hypersensitivity reaction. Successful case reports of desensitization to oxaliplatin have been reported after severe reactions (Gammon, Bhargava, & McCormick, 2004; Meyer, Zuberbier, Worm, Oettle, & Riess, 2002), although some investigators have proposed that patients who develop a severe reaction are unlikely to tolerate additional doses of oxaliplatin (Thomas et al., 2003). Intradermal testing is one method that can be used to predict hypersensitivity reactions with oxaliplatin (Garufi et al., 2003). However, additional studies are needed on the use of desensitization protocols and intradermal skin testing with oxaliplatin.

Biologic anticancer agents also have been associated with hypersensitivity reactions. Cetuximab administration requires antihistamine prophylaxis but still leads to severe reactions in 3% of patients, 90% of which occur during the first infusion (ImClone Systems, Inc., 2008). Severe reactions, including anaphylaxis, bronchospasm, fever, chills, and hypotension, have been reported in about 1% of patients receiving panitumumab (Amgen Inc, 2007a).

Other Toxicities

Alopecia is a common and distressing side effect of many traditional chemotherapy regimens. Evidence suggests that hypothermic scalp regimens may be beneficial (Hesketh et al., 2004), but other options for the management of alopecia are limited. Other colorectal cancer treatment-related toxicities, most commonly associated with bevacizumab, include thromboembolism, bowel perforation, and nephrotic syndrome. A thorough discussion of bevacizumab-associated side effects and their management can be found in Hurwitz and Saini (2006) and Saif and Mehra (2006).

The Role of the Oncology Nurse in Effective Toxicity Management

Oncology nurses play a vital role in the management of side effects associated with chemotherapy and are in a unique position to provide patients with ongoing support and symptom assessment and management. Because the treatment process often is long, nurses can provide support that impacts on the psychological, social, behavioral, and biologic aspects of treatment.

First and foremost, nurses should obtain a baseline history from the patient and establish that the patient understands the potential side effects of therapy. Discovering how well patients have tolerated previous therapy, documenting any allergies and concurrent medications, discovering patients' social support, and understanding their personal coping mechanisms and degree of anxiety are important, as is assessing patients' preferred learning style before planning education regarding their treatment. Successful education hinges on establishing and maintaining a strong partnership between the patient and the oncology team and, in their position as a pivotal contact between the team and the patients, nurses can effectively encourage identification and reporting of early side effects.

Before or at initiation of the first treatment cycle, nurses provide information to patients on the toxicities that are likely to occur and inform patients how to recognize and report early signs and symptoms. This communication can be done through one-on-one teaching, in group sessions, or using a combination of the two. To avoid the development of severe side effects, patients should be encouraged to inform their healthcare team, usually by telephone, of early signs of side effects such as any grade 1 toxicity that does not resolve or even worsens within 24 hours. Oncology nurses also should aim to maintain close communication with patients on a regular basis by telephone. Follow-up telephone calls are particularly crucial during the first cycle of therapy to determine whether patients are experiencing side effects. Additionally, nurses should reinforce recognition and recording of early side effects and symptoms for review at the next follow-up clinic appointment.

Written patient and family education materials, including information about the side effects of drugs, symptom management, easy-to-follow directions on antiemetic regimens, diarrhea management, prevention of cold-induced neuropathy, and skin-care management, should be provided to all patients. Some patients will respond to a simple slide presentation or video emphasizing the anticipated side effects of therapy and appropriate management strategies. Patients should be encouraged to keep treatment diaries to assist with side-effect reporting. Oncology nurses should identify at least one member of the healthcare team whom patients can contact with any questions or concerns.

Effective patient and family education, therefore, plays a key role in the successful recognition and management of treatment-related toxicities in patients with mCRC. As well as assisting patients, oncology nurses can help the healthcare team with the timely recognition and management of side effects, thereby enabling therapy to continue on time and with appropriate dose modification if required. Such interventions can help patients achieve a better clinical outcome and to maintain and improve quality of life for as long as possible. Ultimately, most patients with mCRC will face advanced disease. Treatment may no longer be effective or the patient may decline additional therapy. In this situation, the oncology nurse may have an important role in managing persisting toxicities of previous therapy or advising the patient on potential adverse effects of palliative regimens.

Conclusion

Oncology nurses make an important contribution to the success of chemotherapy for patients with mCRC. Nurses perform detailed assessments, careful planning, and hands-on management during the chemotherapy process. Oncology nurses must continue to update their knowledge of the various chemotherapy regimens available so they can deliver high-quality care and optimize patient safety, comfort, and outcomes.

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