Advanced Colorectal Cancer: Current Treatment and Nursing Management With Economic Considerations

Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP,
Anita Fung, PharmD, and Laura Zitella, NP, AOCN®

Colorectal cancer is one of the most common cancers affecting men and women in the United States. In 2005, 10% of all new cancer cases in men will be colorectal; for women, 11% of new cases will be colorectal. The disease is the third most frequent cancer occurring in both sexes. Colorectal cancer also is the third most frequent cause of death for men and women, and more than 56,000 cancer deaths in 2005 will be attributed to colorectal cancer. Chemotherapy options for treatment of the disease remained relatively stagnant until the approval of irinotecan in 1996 followed by capecitabine, oxaliplatin, and the new targeted agents. The new agents have improved efficacy of treatment for colorectal cancer and the lives of patients with advanced disease. With the new options for treatment come increased nursing and patient-teaching responsibilities, as well as increased costs associated with the newer drugs in the armamentarium of chemotherapy agents. Formulary budgets are seeing dramatic rises in expenditures for the new, targeted therapy treatments; discussion of the most appropriate therapies may be considered. This article will discuss epidemiology of colorectal cancer, treatment options in advanced colorectal cancer, and nursing care crucial to patients undergoing chemotherapy. Discussion of economic impact also will be presented.

The introduction of irinotecan in 1996, followed by the first new platinum analog agent, oxaliplatin, in 2002, offered considerable advances in chemotherapy for advanced and metastatic colorectal cancer (Schrag, 2004). An oral fluorouracil agent, capecitabine, was released in 1998 and has been shown to have activity in colorectal cancer. Two new monoclonal antibody agents, bevacizumab and cetuximab, were approved in 2004 for the treatment of patients with metastatic colorectal cancer. The agents are different in tumor effects and side-effect profiles and may...
be added to conventional chemotherapy for treatment of patients with colorectal cancer. The targeted therapies are unique and expensive. Their addition to hospital formularies may be scrutinized because of added costs. Oncology nurses should know the most recent information about colorectal cancer treatments and be able to safely administer the agents. Knowledge of the potential increase in pharmaceutical costs is essential as well; rising healthcare costs increasingly are under study as providers and institutions struggle to provide quality care under constraints (Ginsburg, 2004).

**Chemotherapy Options for Advanced and Metastatic Colorectal Cancer**

Surgery still is the primary curative modality for the initial treatment of colorectal cancer. Overall, 60%–70% of patients undergoing resection are cured of the disease; those without regional node involvement have a cure rate of 75%–90% (Helm et al., 2003). Recurrences often happen during the first few years after surgery. Recurrence in colorectal cancer usually is not local and often shows up in the liver, lungs, and bone.

**History of 5-Fluorouracil**

5-FU has been the active agent in the treatment of colorectal cancer and has been in use since the 1960s (Midgley & Kerr, 2000b). The drug is a prodrug, a fluorinated analog of uracil. 5-FU achieves its cytotoxic effect by conversion to 5-fluoro-deoxyuridine monophosphate, an inhibitor of thymidylate synthase, which is irreversible (Van Cutsem, Cunningham, Marou, Cervantes, & Glimelius, 2002). It inhibits DNA synthesis and leads to cellular death. 5-FU is one of the oldest drugs in the armamentarium of chemotherapy agents, having first been synthesized in the 1950s (Nicum, Midgley, & Kerr, 2003). Because of the poor oral absorption associated with 5-FU, the drug has been administered most frequently as a bolus injection; however, studies have shown that the drug is a time-dependent agent that causes increased cytotoxicity by prolonging exposure and extending infusion time (Rich et al., 2004). The actual half-life of 5-FU is 8–14 minutes in the plasma, and it is a cell-cycle-specific agent (Nicum et al.).

Modulation of 5-FU has been tried with levamisole and notably folinic acid (leucovorin [LV]). Levamisole has fallen out of favor and has been shown to have no impact on disease-free survival and overall survival when used alone (Andre & de Gramont, 2004). Leucovorin modulates 5-FU by slowing the catabolism of the chemotherapy, essentially prolonging the intracellular activity of the drug (Rich et al., 2004). Researchers have studied numerous 5-FU schedules, including bolus or continuous infusion administration, in an effort to improve efficacy (Rich et al.). LV with 5-FU has become the standard for patients with stage III disease requiring adjuvant therapy, but recent trial results with oxaliplatin challenge that standard (Andre & de Gramont). The drug combination of 5-FU/LV with oxaliplatin or irinotecan plays a prominent role in the treatment of patients with advanced or metastatic colorectal cancer.

**Irinotecan**

Irinotecan (Camptosar®, Pfizer Inc., New York, NY) is a synthetic analog of camptothecan. The significant cytotoxic activity of irinotecan found in patients who previously had received 5-FU indicated that no crossover resistance occurred between 5-FU and irinotecan and prompted approval by the U.S. Food and Drug Administration (FDA) in 1996, initially as second-line chemotherapy for patients who fail or no longer respond to 5-FU–based therapy. Irinotecan now is approved in combination with 5-FU/LV for first-line treatment of advanced colorectal cancer, although it was not recommended in the adjuvant setting in the most recent update of the National Comprehensive Cancer Network (NCCN) guidelines (NCCN, 2005b). The major side effects associated with irinotecan are diarrhea, early and late onset, and neutropenia (Saltz et al., 2000; Wilkinson, 2001).

**Oxaliplatin**

Oxaliplatin (Eloxatin™, Sanofi-Synthelabo, Inc., New York, NY) is a third-generation platinum analog. It exhibits strong synergistic cytotoxic activity with 5-FU. The addition of oxaliplatin to 5-FU/LV (FOLFOX regimen) demonstrated an increase in performance status and overall survival in patients with metastatic colorectal cancer. The combination has become the standard first-line therapy in the palliative setting, and oxaliplatin now is approved in the adjuvant setting as well (Grothey & Goetz, 2004). Side effects associated with oxaliplatin include a dose-limiting neurotoxicity; myelosuppression and gastrointestinal toxicity are less frequent (Berg, 2003).

**Determining Sequence of Chemotherapy for Advanced Colorectal Cancer**

Healthcare providers have several choices in the treatment of patients with advanced or metastatic colorectal cancer. Use of treatment guidelines such as those from the NCCN can help to clarify the role of irinotecan, capcitabine, oxaliplatin, and newer therapies. Combinations of 5-FU/LV with irinotecan or oxaliplatin have been demonstrated as effective therapy for metastatic colorectal cancer; however, clinicians have struggled to answer the question of what is the ideal sequence of therapy.

A phase III trial compared the two treatments in reverse order (FOLFIRI [LV infusion followed by irinotecan then 5-FU bolus and 46-hour infusion of 5-FU] followed by FOLFOLX6 [LV infusion followed by oxaliplatin, then 5-FU bolus and infusion over 46 hours] or the reverse sequence). The researchers found that although both sequences achieved prolonged survival and efficacy, their toxicity profiles were dissimilar. More mucositis, nausea, and vomiting occurred with FOLFIRI, and increased neurosensory toxicity occurred with FOLFOLX6 (Tournigand et al., 2004). Initial choices of future therapy for patients with metastatic colorectal cancer should include rigorous patient assessment. Determining susceptibility for different toxicities and choosing treatment sequences based on patient variability are appropriate. Patients not wanting to endure prolonged or lengthy infusions may decide to opt for...
primary oral therapy. Additional studies are designed to evaluate the treatment question further, and data should be accessible as results become available.

Innovative Targeted Therapies

Although many chemotherapy combinations are available for the treatment of metastatic colorectal cancer, toxicities are associated with many of them. Treating cancer with chemotherapy has become the standard of care, but patients suffer side effects and toxicities from the drugs. In contrast, targeted therapies are directed toward specific pathways involved in tumor growth, maintenance, and metastasis (Meyerhardt & Mayer, 2005). The inhibition of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) has changed standard chemotherapy treatments for metastatic colorectal cancer.

All cells, including cancer cells, require oxygen and nutrition to be viable (Camp-Sorrell, 2003). Angiogenesis (the formation of blood vessels) is necessary for tumors to survive and essential in the formation of metastases (Muehlbauer, 2003; Wray, Riolo, & Ahmad, 2004). A tumor sends out signals to nearby endothelial cells to stimulate new blood vessel growth; if the process is inhibited or disrupted, tumor growth should stop, in theory (Wray et al.). Many new angiogenic growth factors have been identified in colorectal cancer; the new targeted therapies are designed to interfere with tumor blood supply (Muehlbauer; Wray et al.).

Cetuximab (Erbitux™, ImClone Systems Incorporated and Bristol Myers Squibb Company, New York, NY) is a chimeric (a genetically fused product containing mouse and human antibodies) monoclonal antibody that binds to EGFRs that are overexpressed on tumor cells (Ng & Cunningham, 2004). The binding blocks the ability of epidermal growth factor to initiate receptor activation and signaling to the tumor (Punt, 2004). The cellular pathways are necessary for cell proliferation, apoptosis, angiogenesis, adhesion, and motility (Baselga, 2002). Cetuximab is approved as second-line treatment in combination with irinotecan or as a single agent in patients with EGFR-positive, metastatic, irinotecan-refractory colorectal cancer (Punt).

Bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA) is a recombinant humanized monoclonal antibody against the VEGF molecule. It is 93% human and 7% murine and is thought to be less likely to cause an immune response. The antibody prevents VEGF from binding to its natural receptors on the vascular endothelium, which then inhibits VEGF-induced angiogenesis (Fernando & Hurwitz, 2004). Bevacizumab is approved as first-line therapy in combination with 5-FU–based chemotherapy for the treatment of metastatic colorectal cancer.

Since the introduction of 5-FU more than 40 years ago, gradual improvements have been made in the treatment of metastatic colorectal cancer. Newer chemotherapy agents combined with targeted biologic therapy agents have improved response rates, and the overall survival rate for advanced colorectal cancer may approach 24 months. Clinical questions remain as to the optimal sequence and combination of drugs in the treatment of advanced colorectal cancer.

Nursing Management of Patients Receiving Chemotherapy for Advanced Colorectal Cancer

Many of the new agents indicated for the treatment of colorectal cancer have unique toxicity profiles in addition to the traditional side effects of chemotherapy, such as myelosuppression, nausea, vomiting, and diarrhea. Safe administration of therapy for colorectal cancer requires systematic nursing assessment and prompt intervention to prevent or minimize complications. Nurses also play a critical role in educating patients about the potential side effects of therapy and management of the side effects.

Chemotherapy-Induced Diarrhea

Diarrhea is the most common side effect of chemotherapy for colorectal cancer, particularly 5-FU and irinotecan. As many as 80% of patients treated with a 5-FU–based combination regimen develop diarrhea (Benson et al., 2004). Diarrhea is a serious complication that can lead to life-threatening dehydration and electrolyte imbalances. Recently, a multidisciplinary group of experts (11 academic practitioners from varying specialties) developed comprehensive guidelines for the management of chemotherapy-induced diarrhea (Benson et al.). Recommended management begins with detailed assessment of patients, including the number and composition of stools, duration of diarrhea, and associated symptoms such as moderate to severe cramping, nausea and vomiting, decreased performance status, fever, sepsis, neutropenia, frank bleeding, dizziness, abdominal pain and cramping, weakness, and hydration status. Medication profile and dietary history also should be evaluated to identify factors that may contribute to diarrhea. National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 1–2 diarrhea with no other associated symptoms is considered uncomplicated diarrhea, whereas grade 1–2 diarrhea with associated symptoms or grade 3–4 diarrhea is classified as complicated (see Figure 1). Uncomplicated diarrhea may be managed conservatively, whereas complicated diarrhea must be managed aggressively, according to the recommendations in Table 1 (Benson et al.).

Chemotherapy-Induced Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) may be managed according to published guidelines, such as those provided by the NCCN. The most current version of the guidelines can be accessed online at www.nccn.org. Generally, colorectal cancer combination chemotherapy regimens are moderately emetogenic, and antiemetic premedication should include dexamethasone 12 mg by mouth or via IV and a 5-HT, antagonist, preferably palonosetron 0.25 mg via IV (NCCN, 2005a). Palonosetron is the

| Grade 1: increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline |
| Grade 2: increase of 4–6 stools per day over baseline; nocturnal stools; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living (ADL) |
| Grade 3: increase of 6–10 stools per day over baseline; incontinence; IV fluids for dehydration; severe increase in ostomy output compared to baseline; interfering with ADL |
| Grade 4: life-threatening consequences (e.g., hemodynamic collapse) |

Figure 1. National Cancer Institute Common Toxicity Criteria for Diarrhea

Note: Based on information from National Cancer Institute, 1999.
Admit to hospital for
• IV fluids
• Stool evaluation
• Complete blood count and electrolyte panel.

Treatment:
• Antibiotics (fluoroquinolones)
• Octreotide 100 mcg subcutaneously twice a day with dose escalation up to 500 mcg subcutaneously twice a day until the patient has been free of diarrhea for 24 hours
• Chemotherapy should be discontinued and doses should be reduced with subsequent cycles.


table 1. management of chemotherapy-induced diarrhea

<table>
<thead>
<tr>
<th>Grade or occurrence of diarrhea</th>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hours</td>
<td>Instruct patient to&lt;br&gt;• Stop all lactose-containing products, alcohol, and high-osmolar supplements.&lt;br&gt;• Drink 8–10 glasses of liquids daily (such as broth or rehydrating drinks containing electrolyte supplements).&lt;br&gt;• Eat frequent, small meals following the BRAT (bananas, rice, applesauce, toast) diet.&lt;br&gt;Treatment should be initiated with&lt;br&gt;• Loperamide 4 mg by mouth followed by 2 mg every four hours, not to exceed 16 mg daily.&lt;br&gt;• Cytotoxic chemotherapy should be held for grade 2 diarrhea and dose reduction considered for subsequent cycles.&lt;br&gt;If the diarrhea resolves within 24 hours, instruct patient to&lt;br&gt;• Slowly add solid food back into the diet (plain pasta; skinless, white chicken meat; scrambled eggs; and other easily digestible foods).&lt;br&gt;• Avoid cruciferous vegetables such as Brussels sprouts, cabbage, and broccoli.&lt;br&gt;• Avoid milk and milk products for a week after a diarrhea episode because a transient loss of lactase activity may occur in the bowel, resulting in temporary lactose intolerance.&lt;br&gt;• Discontinue loperamide after a 12-hour diarrhea-free interval.</td>
<td>Admit to hospital for&lt;br&gt;• IV fluids&lt;br&gt;• Stool evaluation&lt;br&gt;• Complete blood count and electrolyte panel.</td>
</tr>
<tr>
<td>Grade 1–2 diarrhea persists 24–48 hours.</td>
<td>• Increase loperamide to 2 mg by mouth every two hours.&lt;br&gt;• Start oral antibiotics, preferably with fluoroquinolones.&lt;br&gt;If the diarrhea resolves within 24 hours, instruct patient to&lt;br&gt;• Slowly add solid food back into the diet, as described above.&lt;br&gt;• Discontinue loperamide after a 12-hour diarrhea-free interval.</td>
<td>–</td>
</tr>
<tr>
<td>Grade 1–2 diarrhea persists 48–72 hours.</td>
<td>Evaluate with&lt;br&gt;• Stool workup (e.g., fecal blood, fecal leukocytes, stool cultures)&lt;br&gt;• Complete blood count and electrolytes&lt;br&gt;• Abdominal examination&lt;br&gt;• Fluid and electrolyte replacement.&lt;br&gt;Treatment:&lt;br&gt;• Discontinue loperamide.&lt;br&gt;• Begin second-line agent.&lt;br&gt;– Octreotide (100 mcg subcutaneously twice a day with dose escalation up to 500 mcg subcutaneously twice a day)&lt;br&gt;– Tincture of opium</td>
<td>–</td>
</tr>
<tr>
<td>Grade 1–2 diarrhea progresses to grade 3–4 diarrhea, or patient develops symptoms associated with complicated diarrhea.</td>
<td>• Admit patient to the hospital and treat according to the guidelines for complicated diarrhea.</td>
<td>–</td>
</tr>
</tbody>
</table>

Note. Based on information from Benson et al., 2004; National Cancer Institute, 1999.

only 5-HT3 antagonist that is FDA approved for the prevention of acute and delayed CINV and has a significantly longer half-life than the other commercially available 5-HT3 antagonists (NCCN, 2005a). Patients who are at high risk for delayed CINV or who have experienced significant acute or delayed nausea and vomiting with previous chemotherapy cycles may benefit from the addition of aprepitant as an antiemetic. Aprepitant 125 mg by mouth should be administered one hour before chemotherapy on day 1 with a 5-HT3 antagonist and dexamethasone followed by apreitant 80 mg by mouth and dexamethasone 8 mg by mouth or via IV on days 2 and 3 (NCCN, 2005a).

Recommended agents for the prevention of delayed CINV should continue for two to four days after chemotherapy and depend on which antiemetics were prescribed for the prevention of acute nausea and vomiting prior to chemotherapy. If aprepitant is used, it should be continued with dexamethasone on days 2 and 3. If palonosetron is used, the effect is believed to last for five days because of the long life of the drug (40 hours), and repeat dosing with a 5-HT3 antagonist is not recommended. A recent meta-analysis concluded that the addition of a 5-HT3 receptor antagonist to dexamethasone does not improve the antiemetic effect of dexamethasone for preventing delayed CINV (Huang et al., 2004). Anticipatory nausea and vomiting may be prevented with lorazepam 0.5–2 mg by mouth the night before and morning of chemotherapy (NCCN, 2005a).

Oxaliplatin
The most common adverse effects associated with oxaliplatin are neurotoxicity, fatigue, myelosuppression, nausea, vomiting,
diabetes, and allergic reactions (Andre et al., 2004). Oxaliplatin infusions are administered over two hours and are compatible only with dextrose 5% and water. Oxaliplatin is considered moderately emetogenic.

**Hypersensitivity Reactions**

Hypersensitivity reactions may occur in about 10% of patients receiving oxaliplatin, but less than 3% experience severe reactions (Andre et al., 2004; Dold et al., 2002; Qureshi et al., 2003). The incidence of hypersensitivity reactions increases with repeated dosing, occurring during or shortly after infusion in patients who have received a median of seven infusions (Gammon, Bhargava, & McCormick, 2004). Symptoms range from mild (e.g., transient rash, fever, rigors, urticaria, facial flushing) to severe (e.g., dyspnea, bronchospasm, hypotension, anaphylaxis). If any symptoms of hypersensitivity reaction occur, infusion should be stopped immediately. Mild hypersensitivity reactions may be treated with an antihistamine and corticosteroid; after symptoms resolve, the infusion can be restarted with an extended infusion time of six hours. Moderate or severe hypersensitivity reactions should be managed with epinephrine, corticosteroids, diphenhydramine, bronchodilators, and/or oxygen according to institutional protocols. Patients who experience moderate hypersensitivity reactions can be rechallenged with oxaliplatin on a different day with an extended infusion time of six hours and aggressive premedication including dexamethasone, cimetidine, diphenhydramine, and/or oxygen according to institutional protocols. Patients who experience severe hypersensitivity reactions no longer should be treated with oxaliplatin; others have reported successful retreatment using a desensitization protocol (Gammon et al.).

**Neurotoxicity**

Two distinct neurotoxic syndromes are associated with oxaliplatin: an acute, reversible, peripheral sensory neuropathy and a chronic, cumulative sensory neuropathy. Although neuropathy occurred in 92% of patients treated with the FOLFOX4 regimen (oxaliplatin 85 mg/m² via IV over two hours, day 1, with LV 200 mg/m² via IV over two hours, days 1 and 2, with 5-FU 400 mg/m² via IV bolus, then 600 mg/m² via IV over 22 hours, days 1 and 2, repeated every two weeks [Wilkes, 2005]), most of the episodes were grade 1 or 2 and almost all of the patients reported resolution of their symptoms by one year after treatment (Andre et al., 2004).

Acute neuropathy occurs in 65% of patients (Kemeny et al., 2004) and may begin during infusion but is self-limiting and resolves within 14 days after treatment. Symptoms include paresthesia, dysesthesia, or hypoesthesia (numbness, tingling, or a “pins and needles” sensation) in the hands, feet, perioral area, or throat. Patients also may report jaw spasms, an unusual sensation in the tongue, eye pain, chest pressure, or muscle cramping described as involuntary clenching of the hands, feet, or calves or as the inability to release their grip (Cersosimo, 2005). Acute neuropathy is unusual in that it might be precipitated by exposure to cold temperatures, objects, or liquids. Another manifestation of acute neuropathy is pharyngolaryngeal dysesthesia, a loss of sensation of breathing which presents as an uncomfortable sensation of throat tightness, jaw pain, dysphagia, or dyspnea (Sanofi-Synthelabo Inc., 2004). The sensation usually occurs after ingestion of a cold beverage or ice chips or after inhalation of cold air. Patients describe the sensation as similar to the “brain freeze” experienced after drinking a cold milkshake rapidly, except that the uncomfortable feeling occurs in the throat. Although transient, it can be quite frightening because patients might feel as if they are unable to breathe or catch their breath.

Chronic peripheral neuropathy is dose limiting and cumulative, occurring in 57% of patients (Kemeny et al., 2004) after 6–10 cycles with a cumulative dose ≥ 540 mg/m² (Cersosimo, 2005), but it usually resolves within 6–12 months after completion of therapy (Andre et al., 2004). The peripheral neuropathy is primarily sensory but can progress to sensorimotor. It begins with paresthesia in a stocking-glove distribution, affecting the distal fingertips and toes first and progressing proximally (Wilkes, 2002). In some cases, vibration, proprioception, and temperature sensation may be affected, and the changes can affect activities of daily living that require fine motor coordination, such as buttoning shirts, writing, and typing. Patients should be comprehensively assessed for the presence of peripheral neuropathies.

In a retrospective analysis, the administration of calcium gluconate 1 g and magnesium sulfate 1 g over 15 minutes before and after oxaliplatin administration significantly reduced the incidence and severity of acute and chronic neuropathy (Gamelin et al., 2004). Severe acute neuropathy impairing activities of daily living (NCI-CTC grade 3) occurred in 7% of patients treated with calcium and magnesium infusions compared to 26% of the untreated control group (p = 0.001), and grade 3 chronic neuropathy occurred in 20% of the control group compared to 8% of the treatment group (p = 0.003). A prospective, placebo-controlled, randomized trial is under way to confirm the results. Another strategy that may reduce the incidence of acute neuropathy is to extend infusion time of oxaliplatin to six hours (Giacchetti et al., 2000; Kemeny et al., 2004; Rothenberg et al., 2003). Preliminary studies of pharmacologic agents, including gabapentin 300 mg by mouth three times a day, carabamazepine 400 mg per day, or celecoxib 200 mg by mouth twice a day, have suggested a decreased incidence and/or severity of peripheral neuropathy (Agafitie et al., 2004; Foladore et al 2003; Hoffman, 2004). Based on a review of the available studies evaluating pharmacologic preventive measures, Cersosimo (2005) proposed that calcium and magnesium infusions be considered the first-line option and gabapentin the second-line option for the prevention and treatment of acute oxaliplatin neuropathy. Although limited data exist, the two strategies have demonstrated the most benefit with the least toxicity.

**Capecitabine**

The most common adverse effects of capecitabine are hand-foot syndrome, fatigue, myelosuppression, nausea, vomiting, diarrhea, mucositis, and hyperbilirubinemia (Hoff et al., 2001). Patients should be educated to take capecitabine orally twice a day approximately 12 hours apart within 30 minutes of a meal (Hoff et al.). Capecitabine commonly is prescribed for 14 days followed by a one-week rest period.

**Hand-Foot Syndrome**

Hand-foot syndrome (also known as palmar-plantar erythrodysesthesia) affects more than 50% of patients (see Figure 2) and is characterized by numbness, dysesthesia, paresthesia, tingling, swelling, or erythema (Lassere & Hoff, 2004). Typically, patients experience dysesthesia perceived as a tingling sensation of the palms and soles that progresses within three to four days to a burning pain with swelling and erythema (Lassere & Hoff). It can progress to moist desquamation, blistering, ulceration, or severe pain, which affects the ability to perform activities of daily living (Scheithauer & Blum, 2004). Topical emollients such as lanolin-containing preparations (Bag Balm®, Dairy Association Co., Inc., Lyndonville, VT) (Scheithauer & Blum) or urea-containing preparations such as Eucerin® (Beiersdorfer, A.G., Wilton, CT) (Pendharkar & Goyal, 2004) are helpful for prevention and treatment. Preliminary...
Evidence suggests that celecoxib 400 mg by mouth twice a day during treatment may reduce the incidence of hand-foot syndrome, myelosuppression, and mucositis, although the drug is under scrutiny by the FDA for possible cardiovascular effects (El-Rayes et al., 2004). In a retrospective, case-control analysis of 67 patients to evaluate the effect of celecoxib on the incidence of hand-foot syndrome in patients treated with capecitabine, Lin, Morris, and Ayers (2002) determined that patients who were taking celecoxib concomitantly with capecitabine had a significantly reduced incidence of ≥ grade 1 hand-foot syndrome (12.5% versus 34.3%, p = 0.037) and a non-significant decrease in ≥ grade 2 hand-foot syndrome (3.1% versus 17.1%, p = 0.11). They observed that the incidence of ≥ grade 2 diarrhea also was significantly lower in the capecitabine and celecoxib group (3.1% versus 17.1%, p = 0.11).

Pyridoxine (vitamin B₆) also has been studied at various doses, but randomized, controlled trials are necessary, and its impact on the efficacy of capecitabine is unknown (Lassere & Hoff, 2004; Scheithauer & Blum, 2004). Other agents that warrant further study for the prevention of hand-foot syndrome include nicotine patches, topical dimethyl sulfoxide, and Biafine® (Johnson and Johnson, New Brunswick, NJ), a water-based topical emollient (Scheithauer & Blum).

Because capecitabine is an oral agent that patients self-administer at home, nurses are not present to assess for potential side effects. However, nurses play an important role in patient education regarding potential side effects, symptom management, and when to report symptoms. Despite multiple comfort measures to minimize the discomfort of hand-foot syndrome, the only effective strategy is to interrupt treatment and reduce the dose of capecitabine (see Table 2 and Figure 3).

Irinoctean

Dose-limiting toxicities of irinoctean include delayed-onset diarrhea and neutropenia. Other side effects include acute diarrhea with cholinergic syndrome, nausea, vomiting, anorexia, and mucositis (Cunningham et al., 1998). Oncology nurses must be aware of the impact that severe diarrhea may have for patients with colorectal cancer and intervene accordingly.

Diarrhea

Diarrhea occurs in 50%–80% of patients treated with irinoctean and may be acute or delayed (Barbounis, Koumakis, Vassilomanolakis, Demiri, & Efremidis, 2001). Acute diarrhea occurs within 24 hours of administration and is part of a cholinergic syndrome that also may include rhinitis, hypersalivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. Cholinergic symptoms should be treated with atropine 0.25–1 mg via IV or subcutaneously. Delayed-onset diarrhea can be very severe, leading to life-threatening dehydration and electrolyte imbalances. It occurs a median of five days after every three-week administration and 11 days following weekly administration of irinoctean (Alimonti et al., 2004). The median duration is five to seven days.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Adjustment During a Course of Therapy</th>
<th>Dose Adjustment for Next Treatment (% of Starting Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: numbness, paresthesia, dysesthesia, tingling, painless swelling or erythema of the hands and/or feet, and/or discomfort that does not affect activities of daily living</td>
<td>Maintain dose level.</td>
<td>Maintain dose level.</td>
</tr>
<tr>
<td>Grade 2: painful erythema and swelling of the hands and/or feet, and/or discomfort that interferes with activities of daily living</td>
<td>• First appearance</td>
<td>Interrupt until resolved to grade 0–1. 100%</td>
</tr>
<tr>
<td></td>
<td>• Second appearance</td>
<td>Interrupt until resolved to grade 0–1. 75%</td>
</tr>
<tr>
<td></td>
<td>• Third appearance</td>
<td>Interrupt until resolved to grade 0–1. 50%</td>
</tr>
<tr>
<td></td>
<td>• Fourth appearance</td>
<td>Discontinue treatment permanently. –</td>
</tr>
<tr>
<td>Grade 3: moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet, and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living</td>
<td>• First appearance</td>
<td>Interrupt until resolved to grade 0–1. 75%</td>
</tr>
<tr>
<td></td>
<td>• Second appearance</td>
<td>Interrupt until resolved to grade 0–1. 50%</td>
</tr>
<tr>
<td></td>
<td>• Third appearance</td>
<td>Discontinue treatment permanently. –</td>
</tr>
</tbody>
</table>

Note: Based on information from National Cancer Institute, 1999; Roche Laboratories, Inc., 2003.
Figure 3. Patient Education for the Management of Hand-Foot Syndrome Associated With Capecitabine

Note. Based on information from National Cancer Institute, 1999; Roche Laboratories, Inc., 2003.

Patients should be educated to start loperamide 2 mg at the first episode of diarrhea and to continue loperamide 2 mg by mouth every two hours until diarrhea has resolved for 12 hours. The recommended maximum dose of loperamide is 16 mg per day, but high-dose loperamide (defined as a median of 21 tablets of 2 mg each per day in a trial) has been shown to be safe and effective in patients treated with irinotecan (Abigerges et al., 1994). Another agent that is effective in controlling irinotecan-induced diarrhea refractory to loperamide is octreotide 500 mcg subcutaneously three times a day (Barbounis et al., 2001). A prospective study comparing octreotide 100 mcg versus 500 mcg subcutaneously showed that the 500 mcg dosing was significantly more effective in controlling chemotherapy-induced diarrhea (90% versus 61%, p < 0.05) (Goumas et al., 1998). Octreotide should be discontinued within 24 hours after the resolution of diarrhea to minimize the risk of ileus development.

Bevacizumab

The most common side effects of bevacizumab in phase I and II clinical trials were hypertension, proteinuria, thrombosis, and bleeding (Kabbinavar et al., 2003). In a phase III, randomized, controlled trial comparing irinotecan, bolus 5-FU, and LV (IFL) and IFL plus bevacizumab, only hypertension and gastrointestinal perforation were significantly more common in patients treated with bevacizumab (Hurwitz et al., 2004). Additionally, the FDA sent a postmarketing warning letter updating clinicians about the increased incidence of serious arterial thromboembolic events associated with the use of bevacizumab (FDA, 2005), and the Avastin package insert subsequently was revised (Genentech, Inc., 2005).

Bevacizumab is an extremely well-tolerated monoclonal antibody. Infusion reactions are rare (3%), and standard premedications are not necessary. The infusion-time recommendations state that the first dose should be administered over 90 minutes to detect potential hypersensitivity reactions. If tolerated, the second infusion may be administered over 60 minutes, and the third and all subsequent infusions may be administered over 30 minutes (Genentech, Inc., 2005; Kabbinavar et al., 2003). If a hypersensitivity reaction occurs, premedication with diphenhydramine 50 mcg via IV and a prolonged infusion time minimize the risk of subsequent infusion reactions (Kabbinavar et al.).

Hypertension

Hypertension occurs in 33% of patients and may be managed with standard antihypertensive medications, such as diuretics, angiotensin-converting enzyme inhibitors, calcium-channel blockers, or beta-blockers (Hurwitz et al., 2004). Researchers are attempting to further define the relationship of hypertension as a possible and unusual response to angiogenic growth factors (Sane, Anton, & Brosnihan, 2004). Blood pressure should be monitored routinely prior to the administration of bevacizumab and at least every two to three weeks during treatment.

Proteinuria

Proteinuria was reported as a potential side effect of bevacizumab in phase I and II trials, but the incidence of proteinuria was similar between IFL-treated patients who received bevacizumab and those who did not (Hurwitz et al., 2004). Proteinuria generally is clinically insignificant and reversible after completion of therapy. Nurses can monitor for proteinuria by checking a urine dipstick for protein prior to the administration of bevacizumab and at regular intervals throughout treatment. If a patient develops NCI grade 2 proteinuria (defined as 2+ or higher dipstick reading), a healthcare provider should obtain a 24-hour urine collection for further evaluation. In most Genentech-sponsored clinical trials, bevacizumab was not administered if the 24-hour urine collection showed > 2 g of protein in 24 hours, and the drug was resumed when proteinuria fell below 2 g in 24 hours (Genentech, Inc., 2005).

Gastrointestinal Perforation and Delayed Wound Healing

The antiangiogenesis effect of bevacizumab may delay wound healing by inhibiting dermal wound angiogenesis, so bevacizumab should not be administered within 28 days after surgery or when serious wounds are present. Gastrointestinal perforation occurred in 1.5% of patients treated with bevacizumab in the phase III trial and had variable presentation (Hurwitz et al., 2004). Nurses should assess for the presence of wounds and ensure that all previous surgical incisions are well healed prior to the administration of bevacizumab. Any patient complaint of abdominal pain, especially with vomiting or constipation, should be evaluated promptly.

Cetuximab

Common side effects associated with cetuximab are skin reactions and hypersensitivity reactions (Cunningham et al., 2004). The first infusion should be administered over

Mild epistaxis is the most common bleeding complication, occurring in approximately 50% of patients (Kabbinavar et al., 2003). It generally resolves within five minutes without medical intervention or dose adjustment, and patients should be instructed to apply pressure until bleeding resolves. Gastrointestinal hemorrhage or other serious hemorrhagic complications rarely occur (Hurwitz et al., 2004; Kabbinavar et al.). Thrombotic events occurred more frequently in bevacizumab-treated patients in the phase II trial (19% versus 9%, p value not reported), but the increased incidence was not statistically significant in the phase III trial (19.4% versus 16.2%, p = not significant) (Hurwitz et al.; Kabbinavar et al.). Postmarketing analysis of 1,745 patients in five clinical trials revealed an increased incidence of arterial thromboembolic events (4.4% versus 1.9%), cerebrovascular arterial events (1.9% versus 0.5%), and cardiovascular arterial events (2.1% versus 1.0%) (Genentech, Inc., 2005). Patients who had clinically significant cardiovascular disease, ascites, regular use of aspirin or nonsteroidal anti-inflammatory agents, preexisting bleeding disorders, coagulopathies, need for anticoagulation, or central nervous system metastases were excluded from the clinical trials of bevacizumab (Hurwitz et al.; Kabbinavar et al.). Patients should be assessed for and educated about signs of bleeding or thrombosis (e.g., swelling, pain in leg or calf, abdominal pain, chest pain, dyspnea, syncope, weakness, new onset of severe headache, tachycardia, arrhythmias).
120 minutes, and subsequent infusions may be administered over 60 minutes if patients tolerate the first infusion without hypersensitivity reactions. An inline filter (low protein binding, 0.22 μm) and nonpolyvinyl chloride bag and tubing should be used for administration. Premedication with diphenhydramine 50 mg via IV is recommended to prevent hypersensitivity reactions, but no routine antiemetic premedications are needed (ImClone Systems Incorporated and Bristol-Myers Squibb Company, 2004). If a hypersensitivity reaction occurs, the infusion should be stopped immediately and treatment should be initiated per institutional protocol with epinephrine, corticosteroids, diphenhydramine, bronchodilators, and/or oxygen. Hypersensitivity reactions occur in 20% of patients but rarely are severe (3%), and 90% occur with the first dose (ImClone Systems Incorporated and Bristol-Myers Squibb Company).

**Cutaneous Toxicity**

An acne-like rash occurs in 85% of patients treated with cetuximab, which is characteristic of any agent that inhibits the EGFR pathway (Cunningham et al., 2004; Saltz et al., 2004). EGFR plays an important role in maintaining the integrity of the skin, and skin reactions associated with cetuximab are thought to be inflammatory rather than infectious in nature (Yamamoto, Viale, & Zhao, 2004). The presence and severity of a skin rash are associated with a greater likelihood of response and survival (Cunningham et al., 2004; Saltz et al., 2004).

Patients usually develop a skin rash within three weeks after the start of treatment (Cunningham et al., 2004; Saltz et al., 2004). The rash appears acneiform, follicular, or maculopapular and usually affects the face, chest, and back but generally is not dose limiting (see Figure 4). Less than 10% of patients require dose adjustment for NCI grade 3 or 4 toxicity, defined as a severe rash covering 50% of the body area that may be associated with desquamation or ulceration (see Table 3) (Cunningham et al., 2004). The acne-like rash may improve spontaneously within one to two months without a change in treatment and resolves completely without scarring after treatment is completed (Saltz et al., 2004). Topical antibiotics, topical drying agents, and topical corticosteroids do not appear to affect the course of the rash (Saltz et al., 2004). However, patients should be educated that topical corticosteroids are not recommended because they may increase the potential for infection. Patients also should be encouraged to avoid sun exposure. If a severe rash occurs, dose delays and/or modifications are recommended. Another cutaneous toxicity is a nail disorder characterized by paronychial inflammation; cracking and swelling of the lateral nail folds of the fingers and toes also was seen in 12% of cetuximab-treated patients (Saltz et al., 2004). Unlike the skin rash, the cutaneous toxicity tended to persist throughout treatment and in some patients required several months after therapy to heal completely. Soaking the hands in warm water may relieve discomfort and prevent superinfection (Yamamoto et al., 2004).

**Economic Considerations**

Generic drug alternatives usually are available once a patent life expires, which means the drug is inexpensive to obtain. Because 5-FU has been available since the 1950s, the drug is extremely economical to use; in some cases, it may cost pennies to purchase. Administration of the drug requires nursing time, IV access, and tubing, which add to the overall cost, but the actual drug purchase price is very low. The average wholesale price of 5-FU in a 5 g powder vial ranges from $24.10–$56.00 (Fleming, 2005). The average wholesale prices for newer agents are astounding high and will have a fiscal impact on pharmacy budgets (see Table 4).

The new cancer therapies for advanced colorectal cancer have almost doubled the life expectancy for patients. In a disease that has had very few changes in disease reduction and overall survival, new drugs added to the armamentarium of chemotherapy agents effective in the treatment of advanced colorectal cancer is exciting.

Potent reasons to administer systemic therapy to patients with metastatic colorectal cancer exist. Prior to systemic chemotherapy with 5-FU, the median survival for patients with metastatic colorectal cancer was eight months; with therapy, the number increased to 12 months (Schrag, 2004). With the addition of irinotecan and oxaliplatin, the median survival rose to 21 months, and new agents bevacizumab and cetuximab may further increase the number (Schrag). The accompanying rise in drug expenditure for the newer agents coupled with the sheer numbers of patients with colorectal cancer who would be eligible for treatment with the medications is impressive. In addition to the drug purchase costs, method of delivery (longer infusions which may require hospitalization versus shorter infusion times) may affect therapy costs. Few studies have been published that specifically examine cost-effectiveness of chemotherapy for colorectal cancer; one published article reported that oxaliplatin was acceptable for stage III cancer only if it could reduce mortality by 20% (Koperna & Semmler, 2003).

A British study reported on three chemotherapy treatments, including an economic substudy, for 905 patients with advanced colorectal cancer: de Gramont (LV 200 mg/m² via IV over two hours on days 1 and
2, with 5-FU 400 mg/m² via IV bolus, then 600 mg/m² via IV over 22 hours, days 1 and 2, repeated every two weeks) bolus and infusion 5-FU with folinic acid, protracted venous infusion 5-FU, and raltitrexed (via IV every 21 days) (Hale et al., 2002). Many different factors were assessed with regard to cost in the study, including societal costs, side effects, and drug costs. Whether or not a treatment could be administered in the outpatient setting versus the hospital made a difference in overall costs as well. The researchers concluded that although all three regimens were fairly equivalent in overall survival and response, toxicity differed, with patients receiving protracted infusion having more hand-foot symptoms. The raltitrexed group also had more side effects. With regard to drug and treatment costs, the patients in the de Gramont group had significantly higher costs compared to the other treatments for chemotherapy delivery and societal costs; the finding was attributed partially to the number of patients in the group who were treated in the hospital. The raltitrexed group was lower in costs of pharmacy and nursing time, but the finding was not significant enough to offset the cost of drug acquisition. The group receiving protracted infusion therapy was less expensive to treat overall (Hale et al.).

A study measuring the cost-effectiveness of second-line treatment with irinotecan versus infusional 5-FU alone was reported by a French research group (Levy-Piedbois et al., 2000). The researchers looked at 129 patients receiving 5-FU and 127 patients receiving irinotecan who were treated in an outpatient setting. Although the acquisition costs of irinotecan were much higher than for 5-FU, the researchers concluded that even though the least expensive management for metastatic colorectal cancer was 5-FU, the additional cost of irinotecan was balanced by the added months of survival, with a cost-effectiveness ratio similar to other cancer treatments (Levy-Piedbois et al.).

Another study looked at the clinical and economic benefits of irinotecan in combination with 5-FU and folinic acid as the first-line treatment for metastatic colorectal cancer (Cunningham, Falk, & Jackson, 2002). Each group had two possible chemotherapy-delivery regimens, although the drugs remained 5-FU with LV in treatment arm B, and irinotecan with 5-FU and LV in arm A. The researchers found that in the setting of first-line therapy, the overall costs for each treatment arm represented the total costs that would be associated with first-line therapy and the costs that would be incurred with disease progression, including the possibility of further drug-acquisition costs (Cunningham et al., 2002). They concluded that the cost effectiveness, along with the clinical evidence of improvement in survival benefits, supported the use of irinotecan with 5-FU and LV as first-line therapy for metastatic colorectal cancer (Cunningham et al., 2002).

More research is needed to fully explore the costs associated with chemotherapy treatments for stage III and metastatic colorectal cancer; benefit versus cost is an issue that is becoming more prominent as newer treatments are approved. However, drug costs are not the only aspect to consider; survival benefits versus progression of disease and need for further treatment with chemotherapy agents also factor in to the total economic picture.

### Table 3. Skin Toxicity Associated With Cetuximab

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Macular or papular eruption</td>
<td>Continue treatment. Consider topical agents.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Macular or papular eruption or erythema with pruritus or other symptoms covering &lt; 50% of body surface area</td>
<td>Continue treatment. Consider topical agents.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>One of the following:</td>
<td></td>
</tr>
<tr>
<td>• Symptomatic, generalized macular or papular eruption covering ≥ 50% of the body surface area</td>
<td>Consider treatment with topical or oral clindamycin. Discontinue treatment until the rash resolves to grade 2.</td>
<td></td>
</tr>
<tr>
<td>• Rash or desquamation with confluence</td>
<td>First occurrence</td>
<td></td>
</tr>
<tr>
<td>• Rash or desquamation with pain requiring opioids</td>
<td>Second occurrence</td>
<td></td>
</tr>
<tr>
<td>• Rash or desquamation with erosion of the skin</td>
<td>Third occurrence</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Generalized exfoliative dermatitis or ulcerative dermatitis</td>
<td>Discontinue cetuximab.</td>
</tr>
</tbody>
</table>

Note. Based on information from ImClone Systems Incorporated and Bristol-Myers Squibb Company, 2004.

### Table 4. Average Wholesale Price of Chemotherapy Agents Used in the Treatment of Patients With Colorectal Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lowest Average Wholesale Price ($)</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-fluorouracil, 5 g powdered vial</td>
<td>34.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Leucovorin calcium injection 100 mg, 10 vials</td>
<td>48.00</td>
<td>Yes</td>
</tr>
<tr>
<td>Irinotecan 20 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 ml vial</td>
<td>294.55</td>
<td></td>
</tr>
<tr>
<td>5 ml vial</td>
<td>736.38</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>992.68</td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td>1,985.34</td>
<td></td>
</tr>
<tr>
<td>Capecitabine tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg, 60 tablets</td>
<td>249.20</td>
<td></td>
</tr>
<tr>
<td>500 mg, 120 tablets</td>
<td>1,661.14</td>
<td></td>
</tr>
<tr>
<td>Cetuximab 20 mg/ml, 50 ml vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>576.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab 25 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 ml vial</td>
<td>687.50</td>
<td></td>
</tr>
<tr>
<td>16 ml vial</td>
<td>2,750.00</td>
<td></td>
</tr>
</tbody>
</table>

Note. Based on information from Fleming, 2005.
Cunningham et al. (2004) reported that combining irinotecan and cetuximab for second- and third-line treatment of metastatic colorectal cancer lengthens the median survival time by 1.7 months and that the regimen would cost a little more than $30,000 for an eight-week course of treatment. Adding bevacizumab to 5-FU and LV or irinotecan for eight weeks of therapy totals about $21,000 (Schrag, 2004). The statistics are dramatic and have created concern about increasing chemotherapy costs. The drugs are considerably more expensive than irinotecan, and drug expenditures for the therapies will impact pharmacy budgets significantly. Research examining the cost-effectiveness of the treatments has not been published.

Pharmaceutical Assistance Programs

For patients who meet the income criteria of pharmaceutical companies, assistance programs are available for many of the drugs commonly used in the treatment of patients with metastatic colorectal cancer, including the new biologic agents. Many medication-assistance Web sites may be helpful as resources for enrolling patients in programs designed to help with access to needed drugs (Viale & Mister, 2001). The programs usually require information about a patient’s medical insurance status, income level, and assets, and most require that patients do not have third-party prescription coverage (Chisholm & DiPiro, 2002; Viale & Mister).

Conclusion

Patients with metastatic colorectal cancer have more chemotherapy options than ever before. The numbers of patients who eventually will receive systemic chemotherapy are quite high. The addition of irinotecan to standard 5-FU–based chemotherapy with folinic acid increased the drug expenditure and life expectancy for the treatment of this patient population; with new targeted therapies, the care to be taken with monoclonal antibody agents. Prompt assessment of skin rashes associated with cetuximab and awareness of the potential problems with bleeding and wound healing with bevacizumab are essential to the safe delivery of the agents. With appropriate screening and improved early detection, colorectal cancers may be diagnosed earlier, and for patients with later-stage disease, treatment options have broadened. Oncology nurses should be cognizant of available approved treatments for the disease and administration techniques. Knowledge of the fiscal impact of treatment is important as well.

Author Contact: Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP, can be reached at p.viale@comcast.net, with copy to editor at CJONeditor@jsobel.com.

References


Schrag, D. (2004). The price tag on progress—...

**Rapid Recap**

**Advanced Colorectal Cancer: Current Treatment and Nursing Management With Economic Considerations**

- Advanced colorectal cancer has seen significant progress in the number and type of treatments available as well as a corresponding improvement in length of overall survival.
- The use of new agents in the treatment of advanced colorectal cancer involves increased oncology nursing knowledge in the administration and management of toxicities associated with available treatments.
- New innovative chemotherapy combinations have the potential to increase pharmaceutical formulary budgets because of the cost of newly approved targeted agents in the treatment of advanced or metastatic colorectal cancer.