

Moving Ahead

Challenges With Combination Therapies for Colorectal Cancer

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A continuing education newsletter offered free of charge to nurses

This educational activity is based on a symposium offered in conjunction with the Oncology Nursing Society's 29th Annual Congress.

Novel Challenges Affecting Quality of Life

Barbara A. Barhamand, MS, RN, AOCN

Introduction

These are hopeful times for patients with colorectal cancer (CRC) and the clinicians who treat them. For almost 40 years, regimens based on 5-fluorouracil and leucovorin (5-FU/LV) were the only treatment available.¹ The availability of 5-FU/LV, irinotecan, and oxaliplatin during the course of treatment has improved survival of patients with advanced CRC from a median of about 12 months (with 5-FU/LV alone) to 15 to 21 months.² Recently, the addition of bevacizumab, a new molecularly targeted therapy, to an irinotecan-based therapy (irinotecan plus bolus 5-FU/LV [IFL]) prolonged survival, compared with IFL alone.³ With the commercial availability of bevacizumab and cetuximab (another targeted therapy) and the future availability of currently investigational agents, further improvements in outcome may be achievable.

However, new agents present new challenges. The regimens used to administer these agents are varied and complex. In a recent issue of *The Cancer Letter*, Dr Richard Goldberg, of the University of North Carolina Lineberger Comprehensive Cancer Center, commented that currently available treatments could be combined into as many as 48 different regimens.⁴ Each regimen is associated with side effects that require patient education and side effect management. In addition, each regimen has special administration requirements, and some require special equipment (eg, portable infusion pumps) and frequent clinic visits. Oncology nurses must be prepared to advise patients about these special requirements and to assist them in adjusting to the regimens' demands. As always, nurses must be mindful that patients are individuals and differ in their treatment goals. As new treatments make it possible to lengthen their patients' lives, nurses must remember their role in helping to maintain quality of life.

Epidemiology

CRC continues to be among the most frequently diagnosed cancers in the United States, accounting for 11% of new cancers and 10% of deaths due to cancer in men and women. It is the third leading cancer diagnosis and cause of cancer death in US men and women; 146,940 new cases and 56,730 deaths are anticipated in 2004. Since the 1980s, mortality rates have declined significantly in both sexes (by 1.9% per year between 1987 and 2000 in men and by 1.8% per year between 1984 and 2000 in women).⁵

Historical Perspective

One potential reason for the decline in CRC-related mortality may be the availability of new agents for CRC treatment. The regimens used in CRC are complex and varied. To assist readers in differentiating among them, a regimen table is provided as an insert in this newsletter and online at www.meniscus.com/crc-management/. Information about drug labeling and Food and Drug Administration (FDA) approval history is available at the FDA Web site: <http://www.fda.gov/cder/>.

The first agent used effectively in CRC, 5-fluorouracil (5-FU), was introduced by Heidelberger and colleagues in 1957. The combination of 5-FU and the biochemical modulator leucovorin (LV), 5-FU/LV, was the only treatment option for almost 40 years.¹

After 5-FU, irinotecan was the next agent to become available. It was indicated in 1998 as single-agent therapy for metastatic
(Continued on page 3)

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Target Audience

This educational activity is designed for oncology nurses who care for patients with colorectal cancer (CRC) who are being treated with combination chemotherapies.

Activity Rationale and Purpose

The recent emergence of multiple combination chemotherapeutic regimens for CRC has expanded the treatment options for patients. The increased treatment complexity and unique side effect profiles of new agents greatly affect care management systems and patient lifestyles. The purpose of this newsletter is to provide practical insights into the changing landscape of CRC treatment and the implications for patient education and nursing care.

Learning Objectives



After participating in this activity, nurses should be able to

- Differentiate among chemotherapeutic agents and combination regimens available for the treatment of CRC
- Identify psychosocial and quality of life issues with combination regimens for CRC
- List practical strategies for managing acute and long-term complications of combination regimens for the treatment of CRC

When choosing among continuing education activities, clinicians should select those that are appropriate for their educational needs. Participants in educational activities have the implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional effectiveness. Clinicians should reflect on this activity and its applicability to their own patient population, and then identify and implement appropriate practice changes.

Continuing Education

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Faculty Disclosures

All faculty are expected to disclose any real or apparent conflicts of interest that may have a direct bearing on the subject matter of this continuing education activity. Participants have the responsibility to assess the impact (if any) of the disclosed information on the educational value of the activity. All faculty have been offered a modest honorarium from the accredited provider for their participation in this activity.

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Product Disclosure

Reflecting standard oncology practice, which often requires the off-label or investigational use of some products, this educational activity includes information about many drugs. All faculty participating in continuing education activities are expected to disclose the approved or investigational status (related to the subject matter of this activity—colorectal cancer) of all products and devices under discussion. This information, as of the time of printing, is summarized below. In addition, primary references and full prescribing information should be consulted for complete information. Clinicians have the professional responsibility to ensure that drugs are prescribed and used appropriately, based on their clinical judgment and accepted standards of care.

The following drugs discussed in the newsletter have an FDA-approved labeling indication for the treatment of CRC: bevacizumab, capecitabine, cetuximab, fluorouracil (5-FU), irinotecan, leucovorin, oxaliplatin. The drug FDA approved for indications other than the treatment of CRC is floxuridine.

Adapted from *Drug Facts and Comparisons*. St Louis, Mo: Facts & Comparisons; 2004.



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Case Presentation

Demographics

- Female
- Age 50 years
- Married
- Respiratory therapist

Personal and family history

- Long history of “hemorrhoidal” bleeding
- Mother died at age 47 of CRC

Diagnosis: stage III CRC

Primary treatment: surgery

Adjuvant chemotherapy

- 5-FU/LV × 2 cycles; concomitant 5-FU/LV and radiation therapy; 5-FU/LV × 2 cycles

Diagnosis of recurrent disease, several months off treatment

- CT scan: enlarged periaortic lymph node; rising CEA level

First-line chemotherapy for metastatic CRC

- Enrolled in NCCTG clinical trial N9841
 - Arm A: irinotecan 350 mg/m² q 3 wk
 - Arm B: FOLFOX4 q 2 wk
 - Crossover permitted at progression
- Randomized to Arm A, treated with irinotecan × 5 cycles
- Side effects
 - Neutropenic fever (no growth factors permitted, per protocol)
 - Counts generally recovered before day 1 of each cycle
 - Nausea/vomiting, diarrhea, alopecia
- Disease progression
 - Rising CEA level; metastases to liver

Second-line chemotherapy (NCCTG clinical trial N9841)

- Crossed over to FOLFOX4
 - Side effects
 - Neutropenia after cycle 7, 5-FU dose reduced to level -1
 - Neutropenia after cycle 8, 5-FU dose reduced to level -2
 - Persistent neurotoxicity after cycle 15, oxaliplatin dose reduced to level -1
 - Neutropenia after cycle 25, 5-FU reduced 1 dose level
 - Note: Received trial waiver permitting 3rd 5-FU dose reduction
 - Final 5-FU dosages: 200 mg/m² IV bolus, 340 mg/m² IV infusion
 - Response
 - After 2 cycles, metastatic disease (periaortic lymph node) stabilized
 - 60 cycles of FOLFOX4 administered
 - Off study after 2 1/2 years
 - Patient resented mandated protocol requirements (serial CT scans q 6 wk, lack of access to growth factors)
 - Continued FOLFOX4 off study
 - Disease progression, rising CEA level

Third-line chemotherapy options: capecitabine, bevacizumab, or cetuximab

- Tumor sample sent for EGFR testing
- Treatment decision pending

CRC refractory to 5-FU/LV. An indication for its first-line use in combination with 5-FU/LV followed in 2000. These irinotecan-based regimens differed in the United States and Europe, depending on how 5-FU/LV was administered (bolus or bolus plus continuous infusion). In the United States the IFL, or Saltz bolus 5-FU, regimen was most often used, whereas in Europe an infusional regimen was commonly used.

Single-agent treatment with capecitabine, an oral form of 5-FU, was indicated as first-line therapy in 2001. Clinical trials have shown that as a single agent, capecitabine has activity comparable to that of intravenous 5-FU/LV as first-line treatment for metastatic CRC, although it appears to have little activity as second-line treatment.^{6,7} Some investigators question whether capecitabine can be directly substituted for intravenous 5-FU in combination regimens.⁴ However, the results of a recently published nonrandomized phase II trial combining capecitabine and oxaliplatin are encouraging, and phase III studies evaluat-

ing substitution of capecitabine for intravenous 5-FU/LV in combination regimens are ongoing.⁸

Oxaliplatin, a platinum analogue, was the next agent to be approved. It was indicated as second-line therapy in 2002 and was approved as first-line therapy in 2004. Two additional agents, both monoclonal antibodies (bevacizumab and cetuximab), became available in 2004. Cetuximab targets the epidermal growth factor receptor (EGFR) and is approved only for use in EGFR-positive patients; bevacizumab targets the vascular endothelial growth factor (VEGF). The availability of these new agents has provided many new treatment options for clinicians and patients and presents nurses with many challenges in administering the agents and managing their side effects (see Case Presentation).

Treatment Considerations

Bolus Versus Infusional Regimens

When only 5-FU and LV were available for CRC treatment, researchers attempted to maximize regimen efficacy and tolerability by varying drug dosages and routes and schedules of administration. In the United States, 5-FU and LV were often administered by bolus injection (Roswell Park or Mayo Clinic regimens; see regimen table), whereas in Europe, 5-FU was administered by bolus and infusion (de Gramont [LV5FU2] regimen). In 1997, a study comparing the infusional (LV5FU2) and bolus (Mayo Clinic) regimens reported that the regimens had comparable activity and the infusional regimen was superior in terms of toxicity (lower rate of grade 3/4 toxicity).⁹ A simplified LV5FU2 regimen was then developed, in which bolus 5-FU was administered only on the first day, followed by prolonged administration of high-dose 5-FU.¹⁰ These 2 infusional 5-FU/LV regimens form the basis of many current combination regimens, including irinotecan and oxaliplatin. For example, simplified LV5FU2 plus irinotecan is FOLFIRI (Figure 1); LV5FU2 plus oxaliplatin is FOLFOX4 (Figure 2); and simplified LV5FU2 plus oxaliplatin is FOLFOX6 (investigational) (Figure 3). These regimens are administered every 2 weeks. New regimens are continually being developed.

Infusional 5-FU/LV was also superior to bolus plus infusional 5-FU/LV when administered in a combination regimen. In a recent phase III randomized clinical trial, a regimen combining infusional 5-FU/LV and oxaliplatin (FOLFOX4) was compared with IFL, a regimen based on bolus 5-FU/LV, which was the

Figure 1.—FOLFIRI (investigational regimen). (From André et al.¹¹)

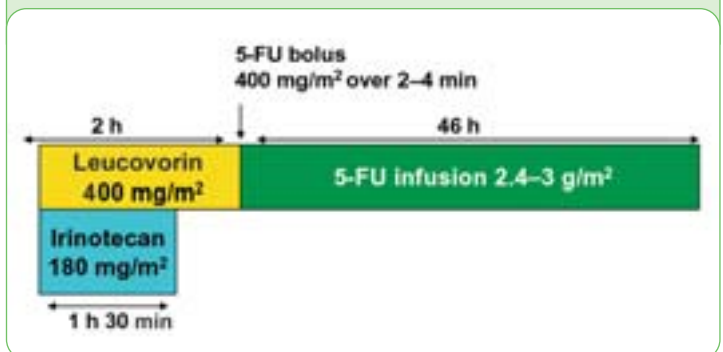


Figure 2.—FOLFOX4. (From oxaliplatin full prescribing information.¹²)

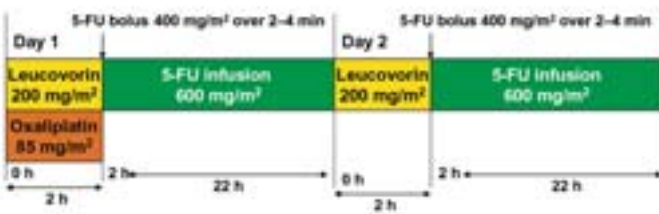
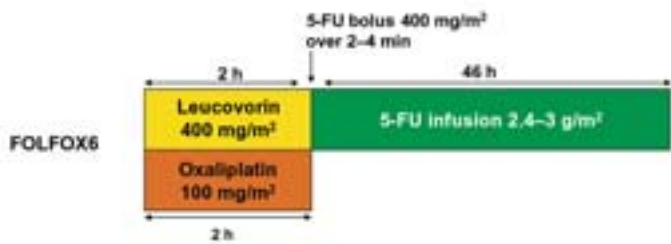


Figure 3.—FOLFOX6 (investigational regimen). (From Maindrault-Goebel et al.¹³)



standard in the United States. Median overall survival was significantly better with FOLFOX4 (19.5 months vs 15.0 months, $P = .0001$).¹⁴ Consequently, the use of infusional regimens, such as FOLFOX4 and FOLFIRI, is increasing in the United States. Increased use has implications for nurses and their patients because infusional regimens have special requirements, including the following:

- Venous access device
- Portable pump
- Time commitment from the patient for several lengthy clinic visits every few weeks

The special requirements of infusional regimens impact the patient's quality of life. Patients may resent the inconvenience of continuous infusions. Being tethered to a pump may make them feel restricted, and they may be concerned that the pump will interfere with even routine daily activities. To help patients feel more comfortable, nurses can suggest that they sleep with the pump under the pillow and shower with the pump hanging outside the shower curtain. Patients may also resent interrupting their lives to schedule several prolonged clinic visits every few weeks. Researchers are attempting to develop regimens that reduce the time commitment required of patients and clinicians (see regimen table insert or online at: <http://www.meniscus.com/crc-management/>). In some of these regimens, capecitabine, an oral form of 5-FU, replaces intravenous 5-FU in combination with irinotecan or oxaliplatin, although capecitabine is currently indicated only for use as a single agent. Other new regimens combine irinotecan and oxaliplatin, with or without 5-FU. Clinical trials are under way to evaluate the tolerability and effectiveness of various combination regimens.

Although the routes of administration of CRC regimens differ, all are associated with treatment-related side effects that impact the patient's quality of life. Nurses must be aware of the side effects associated with the various agents in each combination regimen, to potentially prevent them through appropriate patient education and to manage them if they do occur. Many of the currently used CRC regimens incorporate irinotecan or oxaliplatin.

Irinotecan

Irinotecan has been used for more than 5 years, and its side effects are well documented. They include the following:

- Late-onset diarrhea and neutropenia (the dose-limiting toxicities of irinotecan)
- Nausea and vomiting
- Anorexia
- Mucositis
- Cholinergic syndrome (manifests as cramping, excessive sweating, and increased salivation)

The nurse's role is critical in preventing and managing these side effects, both to maintain the patient's quality of life and to ensure that treatment can continue at recommended dose levels. Patient education is key. To minimize the likelihood of neutropenic fever, nurses can educate patients about the signs and symptoms of neutropenia, and growth factors can be administered. Diarrhea may be serious; deaths due to diarrhea, dehydration, and electrolyte imbalance have occurred.¹⁵ To manage diarrhea, nurses should educate patients to take loperamide at the first sign of diarrhea and continue taking it every 2 hours until free of diarrhea for at least 12 hours. In addition, patients should be instructed to take loperamide at the higher doses listed in the irinotecan package insert, not at the lower doses on the loperamide package. Diarrhea can also be managed with diet. If nausea and vomiting occur, patients can be premedicated with 5-hydroxytryptamine 3 (5-HT₃) blockers, prochlorperazine, or lorazepam. Intravenous or subcutaneous administration of atropine (0.25–1 mg) is suggested for management of the cholinergic syndrome.¹⁶

Oxaliplatin

As previously mentioned, compared with 5-FU/LV therapy alone, the use of 5-FU/LV, irinotecan, and oxaliplatin during the course of treatment has prolonged survival for patients with CRC. Several randomized clinical trials have shown that oxaliplatin improves outcome in advanced CRC. One trial showed that FOLFOX4 (LV5FU2 plus oxaliplatin; see Figure 2) significantly improved median progression-free survival compared with LV5FU2 (9.0 months vs 6.2 months, $P = .0003$).¹⁷ A second trial showed that FOLFOX4 significantly improved median survival time (19.5 months vs 15.0 months, $P = .0001$) compared with IFL, an irinotecan-based regimen.¹⁴ The longest survival times to date were reported in a randomized trial in which an irinotecan-based regimen (FOLFIRI; see Figure 1) and an oxaliplatin-based regimen (FOLFOX6; see Figure 3) were administered sequentially.¹⁸ In this trial, median survival times were prolonged and comparable, regardless of which regimen was administered first: 21.5 months for patients treated with FOLFIRI followed by FOLFOX6, and 20.6 months for patients treated with FOLFOX6 followed by FOLFIRI.

Management of Neurotoxicity

Because oxaliplatin has been available only since 2002, nurses may be less familiar with it than they are with irinotecan. Side effects associated with oxaliplatin and oxaliplatin-based regimens include acute and chronic forms of neurotoxicity.¹² Nursing interventions are key to the prevention and effective management of both forms. The acute form, occurring in 85% to 95% of patients, is generally mild and transient.¹⁹ It consists mainly of sensory symptoms of distal or perioral paresthesia or dysesthesia. Another symptom, pharyngolaryngeal dysesthesia, occurs rarely (in only 1%–2% of patients) and is unique to oxaliplatin. Although breathing is generally not impaired, patients may be frightened by feelings of being unable to breathe, catch their breath, or swallow. To prevent panic, nurses should educate patients before treatment that these symptoms may occur and generally resolve spontaneously. If they do occur, nurses should offer patients something warm to drink. Patients should be encouraged to report symptoms, so nurses can differentiate between acute neurotoxicity and a hypersensitivity reaction (the presence of a cutaneous rash may indicate a hypersensitivity reaction rather than a dysesthesia event).¹⁹

Both nonpharmacologic and pharmacologic interventions can be used to manage oxaliplatin-induced acute sensory neuropathy. Exposure to cold precipitates dysesthesia, so patients should be told to avoid cold foods and beverages (eg, ice cream, iced drinks). Sudden exposure to a blast of cold air (eg, air-conditioned cars or buildings, home freezers) may also precipitate similar problems. Ice chips are sometimes used to prevent 5-FU–induced stomatitis; obviously, this practice should be avoided by patients undergoing oxaliplatin therapy. Patients can decrease exposure to cold by covering their mouths with a scarf during winter months, wearing gloves when they remove items from the freezer, and having someone preheat their car. Patients vary in their need to limit ingestion of cold items; some avoid cold fluids and foods for the entire treatment period, whereas others find that avoiding ingestion of cold items for a few days around the treatment period is sufficient. Patients often learn which events trigger the dysesthesia and adjust their behavior accordingly.²⁰

Pharmacologic interventions, such as pretreatment with magnesium sulfate and calcium gluconate, may also be helpful.²¹ Oxaliplatin-induced acute sensory neuropathy seems to be associated with increased nerve excitability due to disordered nerve ion channels on nerve cell membranes.²⁰ At some institutions, clinicians administer 1 g of calcium gluconate and 1 g of magnesium sulfate 15 minutes before and after each dose of oxaliplatin and have found that this combination alleviates acute neurotoxicity.

In contrast to the acute forms, chronic neurotoxicity associated with oxaliplatin is cumulative and can be dose limiting, although recent reports suggest that neuropathies lessen after therapy is discontinued. Grade 3 peripheral sensory neuropathy was reported in 12% of 1,108 patients treated with FOLFOX4 in a large adjuvant trial, but only 1% of patients still had grade 3 neuropathy after 1 year of follow-up.²² In an attempt to reduce the incidence of oxaliplatin-induced neurotoxicity, investigators are evaluating sequential regimens in which oxali-

platin therapy is interrupted and later reintroduced. This strategy, termed “stop and go,” was evaluated in the OPTIMOX study, which compared continuous oxaliplatin therapy (FOLFOX4) with interrupted oxaliplatin therapy (FOLFOX7 for 6 cycles, simplified LV5FU2 for 12 cycles, then FOLFOX7 for 6 cycles).²³ FOLFOX7 was reintroduced earlier if progression occurred on simplified LV5FU2. Preliminary results suggest that both arms had comparable efficacy and that interruption of therapy improved tolerability (rates of grade 3/4 neurotoxicity

Table 1.—Assessment and Management of Oxaliplatin Cumulative Sensory Neuropathy

At baseline	Assess sensory function Test exteroceptive sensation at hands and feet Fine touch, cotton, pain, pinprick, deep-pressure pain Test proprioceptive sensation Position of limbs, Romberg’s test, perception of passive movements in fingers and toes Perform patient teaching Discuss possible symptoms and the importance of reporting them Explain that symptoms May regress between cycles but may last longer with subsequent doses Usually resolve within 4–6 mo Teach self-care measures to avoid potential injury Stay focused on task at hand Use potholders Use gloves when washing dishes or gardening Inspect skin regularly for cuts, abrasions, burns
After each cycle	Repeat neurologic assessment Question patient about possible functional impairment Assess patient’s ability to perform ADLs; ask patient to perform tasks Button shirt Lace shoes Pick up coins Write several sentences Teach self-care measures, as described above, to avoid injury If impairment is detected, prevent further damage Discuss symptoms with physician before continuing chemotherapy

ADLs = activities of daily living.

Data from Gamelin et al¹⁹ and Wilkes.²⁴

and neutropenia were significantly lower in the FOLFOX7 arm, $P = .0017$ and $P < .009$, respectively, although the rate of grade 3/4 late thrombocytopenia was higher [$P < .0004$].

To maintain the patient's quality of life during oxaliplatin therapy, nurses should assess the patient's neurologic status at baseline and after each treatment cycle. Performing a short, standardized neurologic assessment before therapy is initiated may identify patients with preexisting neurologic deficits who might be poor candidates for oxaliplatin (eg, patients with diabetic neuropathy) and can provide a baseline to detect and monitor neurologic changes. Assessment and management strategies are summarized in Table 1. A more comprehensive discussion appears in an article in the *Clinical Journal of Oncology Nursing*.²⁴

References

Complete references for this article are available online at www.meniscus.com/crc-management/.

Regimen Table

A table including many regimens used in CRC is available as an insert in this newsletter and online at www.meniscus.com/crc-management/.

Moving Ahead With Adjuvant Treatment

Cheryl D. Kosits, MSN, RN, OCN, CCRC

Colorectal Cancer: Epidemiology and Risk Factors

Although colorectal cancer (CRC) is the third most common cancer in both men and women in the United States, incidence declined marginally, by about 3% per year, between 1998 and 2000. These declines may be partly due to increased screening and polyp removal, preventing progression of polyps to invasive cancers. Risk factors for CRC include age (more than 90% of cases are diagnosed in people more than 50 years old) and a personal or family history of CRC, polyps, or inflammatory bowel disease. Modifiable factors associated with CRC include smoking, alcohol consumption, obesity, physical inactivity, a diet high in fat or red meat, and inadequate intake of fruits and vegetables.¹ Unfortunately, CRC is usually asymptomatic in its early stages. Symptoms such as rectal bleeding, blood in the stool, a change in bowel habits, and cramping pain in the lower abdomen may not occur until advanced disease has developed.

CRC sometimes develops in individuals with no risk factors (see Case Presentation), and it is often diagnosed after it has spread beyond the primary site. According to current statistics, 38% of patients are diagnosed with localized disease, 38% with regional disease, and 19% with advanced disease.² Regardless of stage, 83% of patients survive 1 year after diagnosis, 62% survive 5 years, and 57% survive 10 years. For both colon and

rectal cancers, 5-year survival rates increased significantly from 1974–1976 to 1992–1999 (from 50% to 62% and from 49% to 62%, respectively).

Survival decreases with increasing stage of disease at diagnosis. Whereas 90% of patients diagnosed with localized disease survive 5 years, 5-year survival decreases to 66% in patients with regional disease, and to only 9% in patients with advanced disease. Nurses can have an impact on survival rates by taking detailed family histories and by encouraging patients and their families to follow the American Cancer Society (ACS) screening guidelines for CRC, thereby potentially increasing early detection rates.³

Case Presentation

Demographics

- Male
- Age 46 years
- Married
- Fiber optic engineer

Personal and family history

- No identifiable risk factors: younger than 50 years of age; low-fat diet; nonsmoker, nondrinker; no family history of CRC

Symptoms for preceding 10 months

- Weight loss (10 lbs); constipation; sense of incomplete evacuation

Diagnosis

- Adenocarcinoma
- Partially obstructing mass in sigmoid colon (20 cm above anal verge)
- Stage III (T3 N2 M0)

Primary treatment: surgery

Adjuvant chemotherapy

- Enrolled in NSABP trial C07
 - Group 1: modified Roswell Park 5-FU/LV weekly x 6 weeks q 8 weeks
 - Group 2: modified Roswell Park 5-FU/LV + oxaliplatin
- Randomized to group 1, modified Roswell Park 5-FU/LV
 - Side effects \geq grade 2
 - Grade 3 nausea, vomiting, diarrhea
 - Grade 4 dehydration
 - Grade 2 abdominal cramps
 - Completed 3 cycles of treatment, per protocol
 - Cycle 1
 - Admitted to hospital for hydration
 - Completed 4 of 6 weeks of treatment
 - Cycle 2
 - Dose reduction per protocol
 - Side effects controlled, completed all 6 weeks of treatment
 - Cycle 3
 - Side effects controlled, completed all 6 weeks of treatment

Metastatic disease (18 months after primary surgery)

- CEA rising, evidence on CT and PET scans
- Biopsy confirmed liver metastasis (1.7 cm)

First-line chemotherapy

- Enrolled in clinical trial
- Treatment
 - Hepatic resection, floxuridine by HAI, capecitabine, oxaliplatin
- Side effects
 - Mild nausea and vomiting, managed with premedication
 - Myelosuppression, alopecia, slight elevation in liver function tests not requiring dose reduction (floxuridine)
 - Some diarrhea, managed with diet and medication
 - Fatigue and malaise
 - No infection at pump site
 - No functional impairment from neurotoxicity (oxaliplatin)
- Completed treatment 1/2004

No evidence of disease 30 months after primary surgery

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Staging

Four staging systems, Dukes, Astler-Coller, modified Astler-Coller (MAC), and TNM (tumor-node-metastasis), are used for CRC. One of the most commonly used systems, TNM, is based on the depth of invasion of the primary tumor, the number of regional nodes involved with tumor, and the presence or absence of distant metastasis.⁴ Disease without nodal involvement is considered stage I (T1-2 N0) or II (T3-4 N0), and disease with nodal involvement is considered stage III (T1-4 N1-2). The disease is classified as stage IV if distant metastases are present (M1). Unfortunately, even after presumably curative surgical resection of primary disease, about 50% of patients will have a recurrence.⁵ Accurate staging is critical if clinicians are to provide their patients with realistic estimates of risk of recurrence and of length of survival. These issues are discussed in an editorial and 3 articles in the May 15, 2004, issue of the *Journal of Clinical Oncology*.⁶⁻⁹ One tool to assist patients in making decisions about adjuvant therapy for colon cancer is available at the Mayo Clinic Web site at <http://www.mayoclinic.com/calcs>.¹⁰ Estimates of 5-year recurrence-free and overall survival can be obtained by entering the number of positive nodes, depth of tumor (T stage), tumor grade (low or high), and patient's age.

Nursing Considerations

Choice of Therapy

All regimens indicated currently for use in the adjuvant setting are combinations of 5-fluorouracil and leucovorin (5-FU/LV). Adjuvant therapy is usually initiated in patients with stage III (node-positive) disease. Researchers are currently attempting to define the risks associated with earlier-stage disease, and the potential role of capecitabine, irinotecan, and oxaliplatin in the adjuvant setting.⁶ The results of a large, phase III randomized trial (MOSAIC) indicate that the addition of oxaliplatin to 5-FU/LV improves outcome. In the MOSAIC trial, 2,246 patients with stage II or III CRC were randomized to 5-FU/LV or FOLFOX4 for 6 months (12 cycles).¹¹ After 3 years of follow-up, a significantly higher percentage of patients treated with FOLFOX4 were disease free (26.1% vs 21.1%, $P = .002$), corresponding to a 23% reduction in the risk of relapse. Although the reduction in risk was similar in stage II and stage III disease, the administration of adjuvant therapy for stage II disease remains controversial. FOLFOX4 was well tolerated; although 12% of patients experienced grade 3 sensory neuropathy during FOLFOX4 treatment, only 1% still had grade 3 neuropathy after 1 year.

Many clinical trials evaluating newer agents and combinations are being conducted in the adjuvant setting. In some studies, chemotherapy is being administered as neoadjuvant therapy before surgery, to potentially increase tumor resectability, and as adjuvant therapy after surgery. Eligible patients may have the option to enroll in these studies. Information about ongoing trials can be accessed at <http://www.clinicaltrials.gov>.¹²

The 5-FU/LV regimens currently used in the adjuvant setting vary by dose of leucovorin, which is administered at a much higher dose as an infusion than as a bolus injection (200–500 mg/m² vs 20 mg/m²). In contrast, the dose of 5-FU is compa-

rable whether it is administered by bolus or by infusion (400–500 mg/m²). Other differences involve infusion times and scheduling. A short time is required for administration of the Mayo Clinic and 5-FU/LV high-dose regimens, but they are initially administered monthly on sequential days (1–5). In contrast, the infusion time and time between infusions is longer for the Modified Roswell Park and de Gramont regimens. At our institution, clinicians consult with patients and try to select regimens that are most compatible with their schedules and lifestyles.

Although 5-FU/LV combination regimens have been used for many years, nurses must remember that these regimens have side effects. Patients must be taught to anticipate and manage side effects such as nausea and vomiting, diarrhea, dehydration, hand-foot syndrome, and photosensitivity. Because some patients try to maintain their regular patterns despite side effects, such as continuing to eat a high-fiber diet despite diarrhea, nurses must continuously educate them about how best to manage their symptoms. Nurses must also be mindful that patients may experience complications associated with previous surgery or radiation therapy, such as proctitis, diarrhea from adhesions, and enteritis.

Risk of Recurrence or Second Primary

Another important issue for nurses to consider is that patients who have been treated for primary cancer are at high risk for developing recurrent cancer and a second primary.¹³ Although the value of intensive surveillance for recurrent CRC is controversial, monitoring could provide two potential benefits: diagnosis of resectable hepatic metastases, and early treatment of other sites of metastatic disease. Following patients with serial carcinoembryonic antigen (CEA) measurements to detect recurrence seems to be a reasonable approach, whereas routine CT scanning is still controversial.

Genetic Testing

Genetic testing may also be warranted in patients with CRC.¹³ Two major genetic disorders, hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP), are associated with increased risk of CRC. Estimates of the prevalence of HNPCC among patients with CRC range from 0.5% to 13%. A much less common disorder, FAP, results in multiple polyps throughout the colon. The risk of CRC is almost 100% in patients with FAP by the time they reach the age of 40.⁵ If HNPCC or FAP is identified, affected individuals can undergo genetic counseling and their families can undergo genetic testing and be monitored regularly if they are also affected. Women with HNPCC have a higher risk for developing other primary cancers, such as endometrial cancer (30% to 40% risk by age 70), stomach, and ovarian cancer, and develop endometrial and ovarian cancers much earlier (by 10 to 15 years) than women without HNPCC. Therefore, nurses should remind women with CRC to obtain regular gynecologic exams.

Demands of Illness

Both the treatment of CRC and the disease process itself present demands of illness that are associated with numerous events (symptoms, problems, and concerns) that affect

patients and their families. Klemm and colleagues¹⁴ surveyed 121 individuals treated for colon, rectal, or anal cancer to identify the most intense demands. Interestingly, of the top 5 concerns, 4 of them related to psychosocial concerns rather than to symptom- or treatment-related issues. In fact, 90% of respondents reported having psychosocial or existential concerns, and the youngest patients (26–45 years of age) reported greater burden of illness demands than older patients. Demands of illness tended to decrease with time. The authors speculate that patients may have psychosocial concerns because nurses tend to address physical concerns through education about symptom management. To address existential concerns, nurses can assess their patients' perceptions of their disease, ask them about their spiritual and psychosocial concerns, and refer them to spiritual counselors or psychologists.

Management of Hepatic Metastases

If CRC recurs despite adjuvant treatment, there are different treatment options, depending on the site and extent of recurrent disease. The liver is a frequent site of metastasis, reported as the sole or life-limiting component of disease in as many as 60% of patients with CRC.¹⁵ In 1976, autopsy studies in patients who died of CRC indicated that disease remained confined to the liver in about 33%.¹⁶ Surgical resection and systemic chemotherapy are standard treatments for patients with CRC that is confined to the liver. About 65% of these patients are alive and 25% have no detectable cancer 2 years after liver resection.¹⁷ If hepatic metastases could be completely resected, patients with disease confined to the liver could theoretically be cured. In an attempt to increase the resectability of hepatic metastases and potentially increase cure rates, some clinical trials are evaluating the sequential use of chemotherapy before and after hepatic resection. In other trials, chemotherapy is being administered after hepatic resection. Table 1 describes several clinical trials that are planned or ongoing in patients with resectable or resected liver metastases.

Hepatic Arterial Infusion

Hepatic arterial infusion (HAI) chemotherapy is an additional option for patients with disease confined to the liver or when

the liver is the primary site of recurrence. HAI chemotherapy, which is administered directly to the liver via the hepatic artery, may potentially expose hepatic metastases to high drug concentrations, while sparing normal liver tissue. Agents administered by HAI include cisplatin, 5-FU, floxuridine, irinotecan, mitomycin, oxaliplatin, paclitaxel, and vinblastine.¹⁸ Kemeny and colleagues¹⁷ compared HAI administration of floxuridine and dexamethasone plus intravenous 5-FU with or without leucovorin with similar systemic therapy in patients undergoing liver resection for metastatic CRC. After 2 years, HAI chemotherapy significantly improved rates of overall, median, and progression-free survival. The rate of survival free of hepatic recurrence was also significantly better in the HAI group.

Nursing concerns about HAI chemotherapy include care of the pump or access device, as well as management of the complications that occur with this type of therapy, such as pump pocket infection, catheter displacement, thrombosis, chemical hepatitis, and bone marrow toxicity.¹⁹ Patients undergoing HAI who were interviewed by Blair and colleagues²⁰ felt reassured to have liver-directed therapy and they found it convenient. However, they were unable to pursue vigorous activity, their sleep patterns changed, and they scored lower on psychological, social, and spiritual domains than normal volunteers.

Management of Metastatic Disease

In addition to spreading to the liver, CRC spreads locally or distantly through the lymphatic and venous systems. Sites commonly affected include distant lymph nodes, the peritoneum, and the lungs.²¹ To manage metastatic disease, clinicians are using available agents in a variety of regimens, both in the clinic and in the clinical trial setting. Nurses must be knowledgeable about the use of these agents and how they impact the patient's quality of life, when they are administered as single agents or in combination.

Capecitabine

After irinotecan, the first agent to be approved as first-line therapy was capecitabine, an oral form of 5-FU that permits sustained exposure to 5-FU and flexibility in the choice of dosage regimen while avoiding the technical barriers of intravenous

Table 1.—Selected Clinical Trials in CRC With Hepatic Metastases

Disease Stage	Sponsor	Description	No. of Patients	Treatment
IV, resectable liver mets	MDACC	Phase II	80	Oxaliplatin + capecitabine before and after liver resection
IV, resectable liver mets	EORTC	Randomized Phase III	330	Oxaliplatin + 5-FU/LV before and after liver resection vs liver resection alone
IV, resected liver mets	NCCTG	Phase II	15–75	Adjuvant floxuridine + dexamethasone by HAI + oxaliplatin and capecitabine
IV, resected liver mets	MSKCC	Phase II	50	Adjuvant floxuridine + dexamethasone by HAI + irinotecan

Data from ClinicalTrials.gov.¹²

EORTC = European Organization for Research and Treatment of Cancer; HAI = hepatic arterial infusion; MDACC = M. D. Anderson Cancer Center; mets = metastases; MSKCC = Memorial Sloan-Kettering Cancer Center; NCCTG = North Central Cancer Treatment Group.

Table 2.—Nursing Interventions for Capecitabine-Induced Hand-Foot Syndrome (PPE)

Prevention

- Decrease dose and/or decrease drug administration frequency (eg, 21- to 28-day cycle)
- Celecoxib being evaluated for prevention
- Nicotine being evaluated for prevention
- Patient behaviors

Treatment

- Hold drug
- Pyridoxine (vitamin B₆)
- Topical DMSO
- Bag Balm

Nursing role

- Baseline skin assessment, and preassessment before each treatment
- Assess patient self-care ability and need for home support
- Teach patient what to report, when, and to whom
- Teach patient how to minimize PPE development and morbidity

DMSO = dimethyl sulfoxide;
PPE = palmar-plantar erythrodysesthesia.

Table 3.—Patient Teaching Information About PPE

- Reduce friction and heat exposure
- Take short showers with tepid water
- Avoid tight gloves (eg, in dishwashing)
- Avoid pressure on soles and palms
- Avoid jogging, aerobics, jumping
- Avoid squeezing hand (eg, using trowel or knife to cut vegetables, meats)
- Use cool temperatures to relieve tenderness
- Gently apply emollients (eg, Bag Balm)
- Take vitamin B₆ as prescribed
- Take analgesics (eg, acetaminophen)
- Call nurse or physician if palms or soles become red or tender

administration.^{22,23} Capecitabine was compared with bolus 5-FU/LV (Mayo Clinic) in 2 large randomized studies in the first-line setting.^{22,24} In both studies, patients were significantly more likely to respond to capecitabine. By other measures (median times to disease progression, treatment failure, and median overall survival time), the activity of capecitabine was comparable to that of intravenous 5-FU.

Capecitabine is currently indicated as single-agent therapy; the recommended dose is 1,250 mg/m² administered orally twice daily, morning and evening.²³ It is given in 3-week cycles, 2 weeks of treatment followed by a 1-week rest period.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Although some clinicians are substituting capecitabine for intravenous 5-FU in combination regimens, others do not accept its equivalence with intravenous 5-FU in this setting.²⁵ The results of one recent phase II trial combining oxaliplatin and capecitabine are promising,²⁶ but more definitive data are anticipated at the completion of phase III trials.

Considerations with capecitabine include cost (it is expensive), lack of compliance (patients may not take medication as directed), and side effects. Like intravenous 5-FU, capecitabine is associated with palmar-plantar erythrodysesthesia (PPE), which requires careful nursing assessment and management and patient education. Of 596 patients in pooled phase III trials in CRC, 54% reported any grade of PPE, and 17% reported grade 3 PPE.²³ Nursing interventions to prevent, assess, treat, and manage capecitabine-induced PPE are presented in Table 2, and patient teaching information about PPE appears in Table 3. Because some patients may be reluctant to report side effects, nurses should have patients remove their shoes and socks and perform careful skin assessments to identify PPE and prevent PPE progression.

In addition to capecitabine, irinotecan, and oxaliplatin, several other new agents are available for the treatment of CRC. In the next article, Beth Taubes will discuss these agents, their integration into CRC regimens, and future directions in CRC management.

References

Complete references for this article are available online at www.meniscus.com/crc-management/.

Regimen Table

A table including many regimens used in CRC is available as an insert in this newsletter and online at www.meniscus.com/crc-management/.

Doorways to the Future

Beth S. Taubes, BSN, RN, OCN

Today's physicians and patients have many options for the treatment of CRC (see Case Presentation, page 10). With the availability of irinotecan and oxaliplatin, the median survival for patients with metastatic CRC has increased from a range of 11 to 13 months to a range of 14.8 to 21 months.¹ Before the availability of bevacizumab and cetuximab, no treatment options were left once the patient's CRC had become refractory to fluorouracil (5-FU), irinotecan, and oxaliplatin.² With the increased number of agents and regimens from which to choose, it is a challenging task for clinicians to determine the most appropriate therapy for their patients with CRC. In a recent editorial in the *Journal of Clinical Oncology*, Rothenberg and Berlin³ raise some critical issues:

- Is there a strong rationale for combining irinotecan, oxaliplatin, and 5-FU into one regimen, as done in the study reported by Goetz and colleagues⁴?

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Case Presentation (Hypothetical Case)

Demographics

- Male, age 68 years

Personal history

- Weight loss for 1 year; anemic; positive result of stool guaiac

Diagnosis: stage IV (metastatic) CRC

- Nonobstructing lesion in right colon identified by colonoscopy
- Multiple liver metastases on CT scan

Primary treatment

- Surgery was not performed
 - Patient was not a surgical candidate; nonobstructing lesion

First-line chemotherapy

- Enrolled in a phase III randomized clinical trial
 - Capecitabine + oxaliplatin (XELOX)
 - XELOX + bevacizumab 5 mg/kg IV q 14 d
 - FOLFOX4
 - FOLFOX4 + bevacizumab 5 mg/kg IV q 14 d
- Randomized to FOLFOX4 + bevacizumab
 - Administration issues
 - Bevacizumab must be diluted in normal saline
 - Bevacizumab should be given after chemotherapy, but this is not practical, because patients are going home on infusional therapy
 - Administer bevacizumab first, flushing line well before administering oxaliplatin
 - Administer 1 g each of calcium gluconate and magnesium sulfate 15 minutes before and after oxaliplatin to prevent neurotoxicity
 - Premedicate with 5-HT₃ antagonist and dexamethasone to prevent nausea and vomiting
 - Advise patient that a prolonged clinic visit will be required the first time bevacizumab is administered
 - Side effects
 - Transient cold neuropathy (oxaliplatin) managed with patient education
 - Deep vein thrombosis along Mediport catheter, managed with low-molecular-weight heparin
 - Possible causes: advanced cancer or bevacizumab
 - Cycle 8
 - Partial response by CT scan
 - Grade 3 neuropathy; use “stop and go” strategy
 - Hold oxaliplatin
 - Continue 5-FU/LV + bevacizumab
 - Cycle 10
 - Neuropathy improves to grade 1; restart oxaliplatin
- Disease progression after 10 months (20 cycles) of therapy
 - Increase in number and size of liver metastases

Second-line chemotherapy

- Saltz IFL regimen; bolus administration chosen to give the patient a break from infusional therapy
- Disease progression after 3 cycles

Third-line chemotherapy

- Disease refractory to irinotecan; tumor EGFR positive
- Add cetuximab to weekly IFL
 - Acne-like rash, grade 3
- Response for 5 months (19 months since diagnosis)

Fourth-line chemotherapy

- Enroll in a clinical trial

the risk of death.⁶ In a recent phase III randomized trial, however, median survival with FOLFOX4 was significantly better than that with IFL (19.5 months vs 15.0 months, $P = .0001$).⁷ It remains to be seen whether the addition of bevacizumab to oxaliplatin-based regimens will further improve survival.

- What is the optimal means of incorporating cetuximab into treatment regimens?

In a recent issue of *The Cancer Letter*, Richard Kaplan, MD, former chief of NCI's Clinical Investigations Branch, stated that with the use of new agents and new regimens, he anticipates durable responses in patients with CRC, even in those whose disease is not resected.⁸ Areas of investigation include the treatment of hepatic metastases and the administration of chemotherapy before surgery to increase tumor resectability and potentially to prolong survival. Cooperative group trials, such as those listed in Table 1, are planned or already under way to answer at least some of the questions outlined above. Some of these trials will require large numbers of patients, and international cooperation will be needed to recruit them.

In addition to partnering with physicians and patients to select the most appropriate regimens, nurses must consider the impact of these agents and regimens on our clinical practice and on our patients' quality of life. This article describes regimens approved for the treatment of metastatic CRC and the newest agents to be approved, bevacizumab and cetuximab. The results of an audience-response survey conducted at the ONS symposium, on which this newsletter is based, indicate that even experienced oncology nurses need this information. Only 45% of oncology nurses attending this symposium had administered bevacizumab—even fewer (38%) had administered cetuximab.

Agents indicated for use in metastatic CRC include 5-FU/LV, irinotecan, capecitabine, oxaliplatin, bevacizumab, and cetuximab.¹⁰ Capecitabine is indicated in first-line therapy for use as a single oral agent. Cetuximab is indicated in patients with EGFR-positive disease that has become refractory to irinotecan. As shown in Table 2, the other agents have broader indications.

Bevacizumab

Approved by the FDA in February 2004, bevacizumab is indicated in the first-line setting in combination with intravenous 5-FU–based therapy. Bevacizumab inhibits the development of tumor vasculature. For many years, it has been known that tumor growth can be accompanied by increased tumor angiogenesis (ie, the development of new blood vessels).¹⁶ All cells require oxygen and nutrients from the blood to survive; without the development of their own blood vessels, tumors would not be able to grow beyond 1 to 2 mm in size. In the 1970s, Judah Folkman speculated that targeting tumor blood vessel formation might be a useful way to treat human cancer.¹⁶ Folkman and colleagues then attempted to isolate angiogenic factors. The first identified angiogenic factor was named vascular permeability factor; it is now known as vascular endothelial growth factor (VEGF). More recently, several VEGF variants have been discovered. They transmit angiogenic signals into endothelial cells and tumor cells by binding receptors on the cell surface. Different VEGF receptors may mediate different signals; one type of receptor might be important in cell migration, whereas another might induce

- Are these drugs more effective when administered sequentially? Tournigand and colleagues⁵ recently reported a median survival exceeding 20 months in patients treated with FOLFIRI then FOLFOX6 or with the same regimens in the reverse sequence.
- What is the best way to incorporate bevacizumab into CRC regimens? As reported recently in the *New England Journal of Medicine*, the addition of bevacizumab to IFL significantly improved overall survival, compared with IFL plus placebo (20.3 months vs 15.6 months), corresponding to a 34% reduction in

Table 1.—Selected Cooperative Group Clinical Trials in Advanced CRC

Disease Stage	Sponsor	Description	No. of Patients	Treatment
Locally advanced or IV	SWOG	Randomized phase III	2,200	Oxaliplatin + infusional 5-FU/LV ± bevacizumab vs oxaliplatin + capecitabine ± bevacizumab
IV	CALGB	Randomized phase III	2,200	Irinotecan + infusional 5-FU/LV vs irinotecan + infusional 5-FU/LV + cetuximab vs oxaliplatin + infusional 5-FU/LV vs Oxaliplatin + infusional 5-FU/LV + cetuximab
IV, EGFR+	NCIC	Randomized phase III	500	Best supportive care vs cetuximab
IV, irinotecan-refractory	MSKCC	Randomized phase II	150	Cetuximab + bevacizumab + irinotecan vs cetuximab + bevacizumab
IV	NCRI	Randomized phase III	460	Arm I: infusional 5-FU/LV Arm II: oxaliplatin + infusional 5-FU/LV Arm III: capecitabine Arm IV: oxaliplatin + capecitabine

CALGB = Cancer and Leukemia Group B; MSKCC = Memorial Sloan-Kettering Cancer Center; NCIC = National Cancer Institute of Canada; NCRI = National Cancer Research Institute; SWOG = Southwest Oncology Group.

Data from ClinicalTrials.gov.⁹

Table 2.—Indications for Drugs Approved for the Treatment of Metastatic CRC

Drug	Indication	Regimen
Bevacizumab	In combination with 5-FU–based therapy, first line	5 mg/kg as an IV infusion q 14 d
Capecitabine	Single agent, first line	1,250 mg po bid × 2 wk q 3 wk
Cetuximab	EGFR+, irinotecan-refractory CRC Single agent or in combination with irinotecan	400 mg/m ² IV infusion (initial loading dose) 250 mg/m ² IV infusion weekly thereafter
Irinotecan	In combination with 5-FU/LV, first line Single agent in 5-FU–refractory CRC	Saltz regimen* or Douillard regimen* 125 mg/m ² IV weekly × 4 wk q 6 wk 350 mg/m ² IV q 3 wk
Oxaliplatin	In combination with infusional 5-FU/LV, first line	FOLFOX4* (oxaliplatin 85 mg/m ² IV day 1 in combination with LV5FU2* q 2 wk)

*See regimen table in this newsletter or online at www.meniscus.com/crc-management/.

Data from bevacizumab full prescribing information,¹¹ capecitabine full prescribing information,¹² cetuximab full prescribing information,¹³ irinotecan full prescribing information,¹⁴ and oxaliplatin full prescribing information.¹⁵

vascular permeability and cell proliferation.¹⁷ Receptors for VEGF have been identified on many types of tumors as well as on endothelial cells.¹⁶

VEGF, an important factor in blood vessel development, not only promotes tumor growth but may increase the tumor's metastatic potential by providing tumor cells with access to the circulation. Dormant cancer cells can become hypoxic, a process that appears to be an important stimulus of VEGF production.¹⁸ The first step in tumor angiogenesis is the recruitment of new blood vessels from host vessels.¹⁹ This occurs when the wall of the

host capillary degrades, enabling the endothelial cells within the host capillary to migrate outward, forming a tube. The new tumor vessel then forms a connection with the extracellular matrix and recruits pericytes to stabilize the vessel wall.²⁰ This process is driven by proangiogenic factors, such as VEGF, and by other factors, such as degradative enzymes.¹⁷ The acquisition of angiogenic potential by tumors, the “angiogenic switch,” appears to occur early in tumor development and to be a rate-limiting step in tumor progression.²⁰ The tumor vasculature differs from normal vasculature; it is tortuous, leaky, and supported by fewer pericytes than normal vessels.²¹

Bevacizumab is a monoclonal antibody directed at VEGF; it binds to and inhibits VEGF activity. Important facts about the administration of bevacizumab and the side effects associated with it are presented in Table 3. Administration issues of particular concern to nurses include compatibility of agents and diluents, sequence of administration, and duration of infusion.¹¹ When bevacizumab is administered in combination with other chemotherapy agents, compatibility is an important consideration. For example, bevacizumab must be diluted with normal saline, never with dextrose, whereas oxaliplatin must be diluted with dextrose, never with saline. Therefore, if both agents are to be administered, the line must be completely flushed before the second drug is administered.

It is important for nurses administering bevacizumab to be aware of infusion time requirements. Bevacizumab is mixed in 100 mL of normal saline and is run over 90 minutes for the first infusion in order to detect any potential hypersensitivity reactions (an infusion pump is recommended because of the low volume of fluid and the length of the infusion time). If the patient tolerates the first infusion without difficulty, the second infusion is run over 60 minutes and the third, as well as all subsequent infusions, is run over 30 minutes. Patients should be told to anticipate prolonged clinic visits for the first few bevacizumab infusions.

Recent CRC trials have shown a slight increase in vascular side effects (eg, hypertension, bleeding, thrombosis) with the addi-

tion of bevacizumab to standard chemotherapy regimens (ie, irinotecan or oxaliplatin). In the trial comparing IFL plus bevacizumab with IFL alone, hypertension was significantly more frequent in the bevacizumab-containing arm (any grade of hypertension, 22.4% vs 8.3%; $P < .01$; grade 3 hypertension, 11% vs 2.3%; $P < .01$).⁶ In a trial in which bevacizumab was combined with FOLFOX4, slightly higher rates of bleeding, hypertension, and thrombosis were reported in the combination arm, compared with the FOLFOX4-alone arm.²² The rate of grade 3 hemorrhage was 3% for the combination versus 0% for FOLFOX4 alone; rates of grade 3 or 4 hypertension were 8% or 1% for the combination versus 1% (grade 3 only) for FOLFOX4 alone. The rate of grade 3 thrombosis was 3% for the combination versus 1% for FOLFOX4 alone. Serious hemoptysis (in some cases fatal) has also been reported with bevacizumab in patients with non-small cell lung cancer.¹¹ To prevent potential complications, nurses should be alert for potential bleeding problems and should educate their patients for signs and symptoms of bleeding. Blood pressure should be routinely checked and monitored while patients are on bevacizumab therapy. Although hypertension is a common side effect of therapy, it usually can be easily controlled with oral antihypertensive medication.

Proteinuria has also been reported with bevacizumab, and monitoring with serial urinalysis (dipstick) is suggested. Nurses should also be aware that because of the antiangiogenic properties of bevacizumab, wound healing might be delayed. Bevacizumab has a long half-life (20 days) and therefore should not be administered for at least 28 days after surgery.¹¹

Table 3.— Bevacizumab Dosage, Administration, and Side Effects

Dosage	5 mg/kg q 14 d
Infusion time	90 min (1st cycle) 60 min (2nd cycle, if well tolerated) 30 min (3rd cycle and subsequent cycles, if well tolerated)
Properties	Half-life: 20 d
Storage	Refrigerate, protect from light Do not freeze; do not shake Vial contains no preservatives; discard any unused portion
Administration	Do not administer or mix with dextrose solutions Dilute in 100 mL normal saline Diluted drug is stable for up to 8 h if refrigerated
Side effects	Delays wound healing; do not administer for at least 28 d following surgery May cause hemorrhage; patients with recent hemoptysis should not receive bevacizumab May cause hypertension; monitor blood pressure closely May cause proteinuria; monitor with serial urine analysis

From bevacizumab full prescribing information.¹¹

Cetuximab

Like bevacizumab, cetuximab is a monoclonal antibody. Information about the indication, dosage, administration, and side effects associated with cetuximab is presented in Table 4. Whereas bevacizumab is directed against an angiogenic growth factor (VEGF), cetuximab is directed against a growth factor receptor (EGFR). EGFR is a promising target because it is believed to mediate proliferation and many other processes in tumor cells. Cetuximab may inhibit these proliferation and survival signals, and it appears to enhance the sensitivity of tumor cells to chemotherapy.²³ Cetuximab represents an important advance because it offers an additional option to patients refractory to irinotecan: in 2 studies, about 23% of EGFR-positive patients responded to a combination of irinotecan and cetuximab.^{24,25} In addition, a small percentage of chemotherapy-refractory EGFR-positive patients (9% in one phase II study) responded to cetuximab alone.²

Although cetuximab is directed against EGFR, levels of EGFR did not seem to correlate with likelihood of response to cetuximab in clinical trials.²³ In an editorial in the *Journal of Clinical Oncology*, Ellis and Hoff²³ suggest that standards of EGFR positivity must be established. Lack of correlation between EGFR levels and response may be due to activation of alternate or redundant signaling pathways that promote tumor cell survival and inhibit apoptosis despite blockade of EGFR with cetuximab.

Almost all patients treated with cetuximab will develop a rash, and in about 10%, the rash will be severe (grades 3 and 4).¹³

Table 4.—Cetuximab Indications, Dosing, and Administration

Indications	In combination with irinotecan in EGFR-positive metastatic CRC refractory to irinotecan chemotherapy As a single agent in EGFR-positive metastatic CRC in patients who cannot tolerate irinotecan
Initial loading dose	400 mg/m ² (maximum infusion rate 5 mL/min*)
Weekly maintenance dose	250 mg/m ² (maximum infusion rate 5 mL/min*)
Infusion time	120 min (1st cycle) 60 min (2nd and subsequent cycles)
Premedication (recommended)	Antihistamine (eg, diphenhydramine 50 mg IV)
Properties	Clear, colorless solution; may contain easily visible white, amorphous particles of cetuximab
Storage	Refrigerate Do not freeze; do not shake
Administration	Do not dilute Administer with an in-line filter (low protein binding, 0.22- μ M), non-PVC bag and tubing Observe patient for 1 h after administering cetuximab
Side effects	Hypersensitivity reactions Grade 1 and 2 16% with irinotecan + cetuximab 23% with cetuximab alone Grade 3 and 4 3% with irinotecan + cetuximab 2% with cetuximab alone Acne-like rash Grade 1–4 88% with irinotecan + cetuximab Grade 3 and 4 14% with irinotecan + cetuximab

*Reduce the infusion rate by 50% for all subsequent cycles with a grade 1 or 2 infusion reaction. If a grade 3 or 4 infusion reaction occurs, cetuximab should be discontinued immediately and permanently.

From cetuximab full prescribing information.¹³

Patients who develop a rash seem more likely to respond and may survive longer than those with no rash. In one small phase II study of cetuximab alone, median survival was 1.9 months in patients without a rash versus 6.4 months in those with grades 1 and 2 rash and 9.5 months in those with grade 3 rash (grade 0 vs grades 1–3, $P = .02$).² The rash may represent EGFR inhibition in the skin, and although inhibition in normal tissues, such as the skin, may not correlate with inhibition in the tumor, lack of a rash may indicate failure to inhibit EGFR in the tumor.²³ Ellis and Hoff speculate that the dose of anti-EGFR therapy might be escalated until the rash is observed. However, the rash may negatively impact the self-image of patients already struggling with many other demands of illness.

Nursing interventions to alleviate the rash include advising patients to avoid sun exposure and to use topical antibiotic creams. Cetuximab therapy may also be interrupted, although this approach may be counterproductive if the rash does represent EGFR inhibition; therefore, it is important for nurses to support and educate their patients through this phase. In a phase II single-agent cetuximab study, many patients noted some degree of spontaneous improvement in the first 2 months of therapy without dose modification.²

The results of ongoing and planned clinical trials will help establish the optimal use of cetuximab in the treatment of metastatic CRC. The FDA required 2 large (1,500 patients each) survival trials as part of accelerated approval for cetuximab in metastatic CRC.²⁶ One trial (EPIC) compares cetuximab as a single agent versus cetuximab plus irinotecan, and the second (EXPLORE) compares cetuximab as a single agent versus cetuximab plus oxaliplatin.

Conclusions

The availability of new agents has prolonged survival of patients with metastatic CRC. As nurses, we must educate ourselves about new therapeutic approaches and their impact on the lives of our patients. As our patients survive longer, we have the opportunity to improve the quality of their lives by assessing and monitoring our patients, providing appropriate patient education, and managing therapy-induced side effects.

References

Complete references for this article are available online at www.meniscus.com/crc-management/.

Regimen Table

A table including many regimens used in CRC is available as an insert in this newsletter and online at www.meniscus.com/crc-management/.

Learning Assessment

Moving Ahead: Challenges With Combination Therapies for Colorectal Cancer

To receive continuing education credit, you must read this publication, score at least 70% on the learning assessment, and submit the evaluation form on page 15 via fax, mail, or online to the Meniscus Educational Institute.

- Compared with bolus 5-fluorouracil (5-FU)-based regimens, the use of infusional 5-FU/LV regimens is increasing in the United States because
 - the infusional 5-FU regimen (de Gramont, LV5FU2) is more effective than the bolus regimen (Mayo Clinic)
 - infusional 5-FU/LV regimens are more tolerable and appear to have more activity in combination than bolus regimens
 - clinic visits are shorter with infusional regimens
 - patients prefer infusional regimens because they have less impact on their quality of life than bolus regimens
- Nursing interventions to manage irinotecan-induced diarrhea include administration of loperamide
 - as directed on the package label, after the patient has had loose stools for 24 hours
 - as directed on the package label, starting with the first dose of irinotecan
 - at higher doses than recommended on the package label, at the first sign of diarrhea
 - at higher doses than recommended on the package label, after the patient has had loose stools for 24 hours
- Following administration of oxaliplatin, a clinic patient begins to panic, feeling unable to breathe or swallow. Pulse oximetry indicates normal oxygen saturation. After reassuring the patient, what is the best nursing intervention to initiate?
 - administer 10 mg morphine sulfate IV push
 - start an IV of normal saline
 - initiate oxygen therapy at 2 L by nasal cannula
 - offer a cup of hot tea or hot chocolate
- Which of the following would be an appropriate nursing strategy to manage neurotoxicity associated with oxaliplatin?
 - discouraging caffeine intake to decrease neuroexcitability
 - offering ice water to ease symptoms of pharyngolaryngeal dysesthesia
 - conducting serial neurologic examinations to detect neurotoxicity and minimize impact on activities of daily living
 - advising patients to increase their potassium levels by eating more bananas
- A patient recently diagnosed with stage III colorectal cancer has asked about treatment options after surgery. Which adjuvant therapy options are indicated outside the context of a clinical trial?
 - oxaliplatin and infusional 5-FU/LV (FOLFOX)
 - irinotecan and infusional 5-FU/LV (FOLFIRI)
 - oxaliplatin or irinotecan in combination with oral 5-FU (capecitabine)
 - regimens containing 5-FU/LV alone
- A patient is receiving hepatic arterial infusion (HAI) for hepatic metastases of colorectal cancer (CRC). Which of the following is an appropriate nursing intervention?
 - check catheter for displacement
 - assess patient for neurologic deficit
 - encourage aerobic exercise for increasing metabolism
 - restrict fluid intake to 500 mL per day
- Which of the following is a *true* statement about CRC metastatic to the liver?
 - hepatic resection of liver metastases is never curative
 - HAI is a route of chemotherapy administration that is not beneficial and is no longer used
 - chemotherapy administered before and after surgical resection of hepatic metastases is being evaluated as a potential means to increase resectability and increase cure rates
 - liver metastases are not an important concern in patients with CRC, because CRC infrequently metastasizes to the liver
- Which of the following options is an important component of a teaching plan for patients receiving capecitabine?
 - frequent hot showers will reduce the likelihood of cutaneous hand-foot syndrome
 - a loofah sponge is helpful to increase circulation in the hands and feet
 - weight-bearing exercise, such as jogging, will help maintain muscle tone
 - regular use of emollients, such as Bag Balm and lanolin, will maintain skin integrity
- Bevacizumab is indicated
 - in combination with 5-FU-based therapy as adjuvant treatment for CRC
 - in combination with 5-FU-based therapy for the treatment of metastatic CRC
 - as a single agent for the treatment of metastatic CRC
 - in combination with cetuximab for the treatment of metastatic CRC
- One important consideration in the administration of combination therapy including bevacizumab is
 - compatibility with diluents and other agents
 - the need to administer bevacizumab with food
 - that irinotecan cannot be administered with bevacizumab
 - that oxaliplatin cannot be administered with bevacizumab
- A patient with metastatic CRC read about monoclonal antibody therapy in a news article and asks about receiving cetuximab. Which of the following would be an important point to discuss with this patient?
 - it cannot be used in combination with any other agent
 - it is used in patients with tumors that overexpress the vascular endothelial growth factor receptor (VEGFR)
 - its use is currently restricted to patients with epidermal growth factor receptor–positive disease
 - it has increased blood pressure in many patients
- The acne-like skin rash associated with cetuximab
 - is rare and does not impact quality of life
 - may potentiate the effects of the vascular endothelial growth factor in the skin
 - signals a life threatening reaction; when it occurs, cetuximab must be discontinued immediately
 - has been associated with response and prolonged survival in some clinical trials

Evaluation Form

Moving Ahead: Challenges With Combination Therapies for Colorectal Cancer

CE Activity Number and Credit

Nursing: 6276-0411NN (1.5 contact hours)
Project: 6276

For online registration and submission, go to www.meniscus.com/eval/crc-management/.

Submit this form by August 31, 2005:

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Nurse Other _____

Mailing address for statement of credit _____

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Evaluation	Excellent	Good	Satisfactory	Poor
Accuracy and timeliness of the content	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Relevance to your daily practice	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Freedom from commercial bias	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Extent to which learning objectives were met	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Overall quality of this activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Usefulness of learning materials as future reference	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Answers	a	b	c	d
1.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

What is the most important thing you learned from this activity? (check all that apply)
 Current treatment options Diagnostic strategies Quality of life issues
 Clinical trial information New treatment options Side effect management
 Other _____

What questions do you still have regarding this topic? (check all that apply)
 Clinical trial information Pharmacoeconomics None
 Side effect management Applicability to other populations Other _____

Why did you participate in this activity? (check all that apply)
 Amount of CE credit Convenience Format (live, Internet, CD-ROM, etc)
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Moving Ahead

Challenges With Combination Therapies
for Colorectal Cancer

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