

Expanded Treatment Options in the Adjuvant Therapy of Colon Cancer: Implications for Oncology Nurses

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Purpose/Objectives: To review the role of adjuvant therapy in the treatment of patients with colon cancer.

Data Sources: Published articles, Internet sources, and books.

Data Synthesis: Colon cancer is a very common cancer in men and women. Chemotherapy, consisting primarily of 5-fluorouracil, has been used to treat colon cancer since the 1950s, but additional effective agents against metastatic disease now are available. The options for adjuvant chemotherapy have increased dramatically. Ongoing studies are evaluating the role of biologics in adjuvant therapy of colon cancer.

Conclusions: Use of oxaliplatin in the adjuvant setting has further defined exciting new therapy options for patients with colon cancer.

Implications for Nursing: Oncology nurses caring for patients with colon cancer should be aware of new changes in therapy options. Although the addition of new therapies increases the tools in the drug arsenal for the common disease, management of toxicities of therapy is crucial as well. This article reviews changes in therapy options and toxicity management, including discussion of key issues for oncology nurses in the care of patients with colon cancer.

Colon cancer is the third most common cancer in men and women in the United States. The disease is one of the leading causes of cancer mortality and is responsible for about 200,000 deaths per year in Europe and the United States (Nicum, Midgley, & Kerr, 2003). Although the cancer occurs frequently, the death rate has decreased since the mid-1980s, probably because of a combination of factors, including better screening and earlier detection and, more recently, improved treatments (Sargent & Murphy, 2003). Chemotherapy options for patients diagnosed with advanced and metastatic disease have changed considerably. In addition to the approval of several new agents for metastatic colon cancer that have increased patient survival, effective new adjuvant therapy options have become available. The U.S. Food and Drug Administration (FDA) has approved new therapeutic approaches that are further improving survival in this population of patients.

Pathogenesis of Colon Cancer

A sequence of events has to occur for individuals to develop colon cancer; the disease generally develops over decades with multiple genetic occurrences (Williams et al., 2003). Adenomas undergo changes that may cause development into carcinomas (Nicum et al., 2003). Because the process can take many years, screening for colon cancer is of the utmost importance.

Key Points . . .

- ▶ Colon cancer is the third most common cancer in men and women in the United States.
- ▶ More than half of patients with colon cancer who show no sign of macroscopic disease after surgery die of recurrence or distant metastasis.
- ▶ Recent trial results have shown considerable improvement in patients with colon cancer receiving adjuvant therapy with oxaliplatin-based chemotherapy.
- ▶ Oxaliplatin recently was approved by the U.S. Food and Drug Administration for the adjuvant treatment of patients with colon cancer, and oncology nurses should be aware of treatment advances for this population.

Adenocarcinomas are malignant tumors of epithelial origin, stemming from the glandular epithelium of the colon mucosa. Adenocarcinomas infiltrate the tissue, moving into muscularis mucosae, the submucosa, and, if not removed, the muscularis propria. The tumors may present as well, moderately, or poorly differentiated. About 15% of colon cancers occur in inherited patterns, including familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer. One of the initiating steps in colon carcinogenesis may be a mutation of the adenomatous polyposis coli tumor suppressor gene (the cause of FAP) (Williams et al.). Further identification of genes involved in the pathogenesis of colon cancer is under way.

Risk Factors for Colon Cancer

Risk factors for colon cancer are varied; family history, age, gender, and ethnicity have been implicated (Sargent & Murphy, 2003). The disease affects more men than women and is found

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more often in African American women than in white women (Sargent & Murphy). The role of ethnicity has been studied, and an increased incidence of colon cancer has been found in African Americans and people of Jewish, Eastern European, or Hispanic descent (Sargent & Murphy). Personal history of polyps or inflammatory bowel disease and hereditary syndromes can increase the risk of developing colon cancer (Jemal et al., 2005). Modifiable risk factors include a diet high in animal fat or red meat, a folate-deficient diet, a sedentary lifestyle, obesity, and smoking (Nicum et al., 2003).

Screening for Colon Cancer

Although screening guidelines exist for detecting colon cancer (see Figure 1), the nationwide prevalence of colon screening is approximately 50% (Smith, Cokkinides, & Eyre, 2004). The American Cancer Society recommends that individuals at higher risk because of personal history of adenomatous polyps, personal history of curative-intent resection of colon cancer, family history of colon cancer or colon adenomas diagnosed in a first-degree relative before age 60, personal history of inflammatory bowel disease, or family history or genetic testing validating the presence of hereditary syndromes receive more intensive surveillance (Jemal et al., 2005).

Discussion is ongoing about ideal strategies for screening and whether colonoscopy reasonably can serve as the dominant screening test or whether less costly techniques are adequate (Jemal et al., 2005). After diagnosis of polyps by colonoscopy, debate exists about appropriate surveillance. A recent study showed that surveillance colonoscopy may be overused, affecting healthcare cost resources (Mysliwiec, Brown, Klabunde, & Ransohoff, 2004). The use of computed tomographic colonography also has been studied in the detection of colon neoplasms in an average-risk screening population. One study found it to be accurate, with an outcome similar to that of standard colonoscopy; however, once a polyp or lesion is discovered, colonoscopy must be performed (Mahon, 2004; Pickhardt et al., 2003).

Signs and Symptoms of Colon Cancer

Common signs and symptoms of colon cancer are variable. The first thing patients may notice is blood in the stool that may be mistaken for hemorrhoids (Sargent & Murphy, 2003).

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- Fecal occult blood test (FOBT) annually
 - Flexible sigmoidoscopy every five years
 - FOBT annually and flexible sigmoidoscopy every five years
 - Double-contrast barium enema every five years
 - Colonoscopy every 10 years

Immunochemical stool screening is an alternative test to the stool guaiac examination and uses monoclonal and/or polyclonal antibodies to determine the presence of the global protein portion of human hemoglobin, thus eliminating the need for dietary restriction (Levin et al., 2003).

Figure 1. Screening Guidelines for Colon Cancer in Asymptomatic Men and Women at Average Risk (Starting at Age 50)

Note. Based on information from Smith et al., 2004.

The physical location of a tumor may correspond to a specific symptom complex (see Figure 2). In some cases, patients may present with partial or complete bowel obstruction from the tumor, which reduces the five-year survival rate to 31%, compared with 72% for those without obstruction (Skibber, Minsky, & Hoff, 2001).

Staging of Colon Cancer

Once a diagnosis of colon cancer is made, the tumor is staged pathologically. Staging helps to determine treatment options based on the extent of disease and prediction of recurrence. The earliest staging system for colon cancer, introduced in 1932, is the Dukes' Classification System, which uses a letter system (A, B, C, and D) to denote tumor depth and invasion. Another staging system, the Astler-Coller System, was proposed in 1954. For ease and simplicity, the tumor, node, metastasis (TNM) system is used by most in the staging of colon cancer (see Figure 3), although the Dukes' Classification System still is seen in practice (see Table 1). The most important prognostic indicator for colon cancer is pathologic stage at diagnosis (Meyerhardt & Mayer, 2005). According to the College of American Pathologists, optimal node sampling is crucial, and more than 12 lymph nodes should be analyzed (O'Connell, 2004). Some healthcare providers believe that 14–17 lymph nodes should be obtained for optimal results (Zaniboni & Labianca, 2004). Once the cancer is staged, survival can be estimated and treatment options determined. Although the five-year survival rate for stage I colon cancer is about 93%, the rate drops to 8% for patients presenting with stage IV disease. Patients presenting with stage IIIA colon cancer have a five-year survival rate of 83%; survival for stage IIIB drops significantly to 64%; for those with stage IIIC, the rate is a sobering 44% (O'Connell, Maggard, & Ko, 2004).

Treatment of Colon Cancer

For patients with colon cancer, whether advanced, metastatic, or in the adjuvant setting, chemotherapy treatments remained fairly similar for decades: 5-fluorouracil (5-FU) in various infusion regimens. 5-FU is a prodrug, a drug that is a pharmacologically inactive derivative of an active drug. Prodrugs are converted to active form through enzymatic or nonenzymatic pathways (Backes, 2001). 5-FU is converted intracellularly into different active metabolites that inhibit cellular synthesis of thymidine, DNA, and RNA. Because of this action, 5-FU is a cell-cycle-specific agent, primarily S-phase (Midgley & Kerr, 2000). However, since the late 1990s, treatment options beyond and in combination with 5-FU have significantly increased for patients with advanced and metastatic disease (stage IV). Patients with stage II and III colon cancer who needed adjuvant therapy remained a challenge. However, recent data have yielded important new information that has changed standard adjuvant therapy for this patient population. The evolution of adjuvant therapy is depicted in Figure 4.

Adjuvant Therapy

Adjuvant therapy refers to chemotherapy or radiation therapy administered to patients who have undergone primary treatment, usually potentially curative surgical resection. Adjuvant treatment is given to increase the chances of long-term cure, essentially treating any micrometastases that remain

Ascending Colon Tumor

Abdominal aching with anemia or iron deficiency weakness
Occult blood in the stool
Possible right, lower abdominal mass
Weight loss

Transverse Colon Tumor

Occult blood in the stool with constipation
Feeling of fullness in the abdomen
Crampy abdominal pain

Descending Colon Tumor

Bright red blood per rectum
Stools of ribbon-like consistency
Feeling of straining at the stool (tenesmus)

General symptoms include rectal bleeding, occult blood in the stool, and a change in bowel habits, such as constipation or diarrhea, pain in the abdomen, nausea and vomiting, and unexplained weight loss or anemia.

Figure 2. Signs and Symptoms of Colon Cancer by Site of Presentation

Note. Based on information from Sargent & Murphy, 2003; Skibber et al., 2001.

after surgery (Waters, 2004). More than half of patients with no macroscopic sign of residual tumor postoperatively die of recurrence or distant metastasis to the liver, lungs, or bone. Therefore, adjuvant therapy is of considerable importance in the management of colon cancer (Nicum et al., 2003; Midgley & Kerr, 2000).

For 40 years, adjuvant therapy consisted of different versions of 5-FU-based chemotherapy; however, exciting advances in oxaliplatin-based chemotherapy in conjunction with 5-FU have changed the treatment paradigm (Meyerhardt & Mayer, 2005). Originally, adding variations of leucovorin or levamisole allowed for biochemical modulation of 5-FU; the intervention improved efficacy of the original chemotherapy agent (O'Connell, 2004). Levamisole originally was shown to significantly extend time to tumor recurrence and overall survival in a study of 1,296 patients with stage III colon cancer and became the standard of care in 1990 (Moertel et al., 1990). Levamisole showed no improvement alone, but, in combination with 5-FU, the therapy reduced the risk of cancer recurrence by 41%, with the overall death rate reduced by 33%. However, in subsequent trials, leucovorin (or folinic acid) was determined to be most successful in increasing thymidylate synthase inhibition, improving response rates from 11% to 23% in patients with metastatic colon cancer (Nicum et al., 2003). The Intergrup-0089 trial studied

adjuvant chemotherapy for high-risk stage II and stage III colon cancer and found that when levamisole was added to 5-FU and leucovorin, the combination of the three drugs was not superior to 5-FU and leucovorin alone and that six months of therapy with 5-FU plus leucovorin should become the standard adjuvant treatment for patients with resected, high-risk colon cancer (Haller, Catalano, Macdonald, & Mayer, 1998). Therefore, standard duration of adjuvant therapy could be reduced safely from 12 to 6 months (Cascinu et al., 2003; Di Costanzo et al., 2003; O'Connell).

A recent update of 5-FU modulation with leucovorin, with analysis of data from 3,300 patients, validated that the combination improves response rate and overall survival in patients with advanced colon cancer compared with 5-FU alone (Thirion et al., 2004). Poplin et al. (2005) provided further confirmation of the lack of benefit of adding levamisole to 5-FU, either in continuous infusion or bolus administration.

Previously, patients with stage II disease were not considered for standard adjuvant chemotherapy unless poor prognostic factors existed, such as those identified in the American Society of Clinical Oncology (ASCO) guidelines for treating this population of patients (Benson, Schrag, et al., 2004). The guidelines were created in collaboration with the Cancer Care Ontario Practice (CCOP) Guideline Initiative. Patients considered at higher risk were those with inadequately sampled nodes during surgical resection (a larger number of examined lymph nodes is associated with better overall survival), poorly differentiated histology, or T4 lesions or perforation (Benson, Schrag, et al.; Rao & Cunningham, 2003). Presently, ASCO has no guidelines for the management of stage III colon cancer, and the CCOP guidelines for stage III patients have not been updated since 2000.

Other attempts to improve efficacy of adjuvant therapy include modulation of infusional administration of chemotherapy, particularly from bolus to protracted infusion

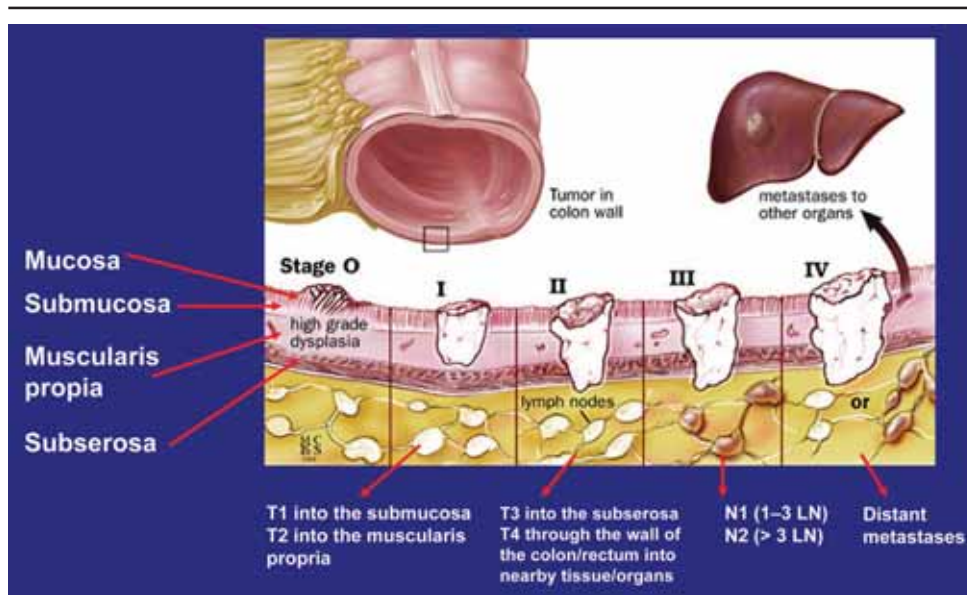


Figure 3. Tumor, Node, Metastasis Staging of Colon Cancer

Note. From "Hereditary Colorectal Cancer: Staging of Colon Cancer" by the Johns Hopkins Gastroenterology and Hepatology Resource Center, <http://www.hopkins-gi.org>. Copyright 2005 by Johns Hopkins University. All rights reserved. Reprinted with permission.

Table 1. Tumor, Node, Metastasis (TNM) Staging and Dukes' Classification System Equivalents

TNM Stage	TNM Criteria	Dukes' Stage
0	Tis, N0, M0	Not applicable
I	T1, N0, M0 T2, N0, M0	A
II	T3, N0, M0 T4, N0, M0	B
III	Any T, N1, M0 Any T, N2, M0	C
IV	Any T, any N, M1	D
Stage IIA	Primary tumor is T3.	–
Stage IIB	Primary tumor is T4.	–
Stage IIIA	T1–T2, N1, M0	–
Stage IIIB	T3–T4, N1, M0	–
Stage IIIC	Any T, N2, M0	–

Note. Based on information from Greene et al., 2002; Skibber et al., 2001.

techniques. Because 5-FU has a very short half-life in the plasma and is cell-cycle specific, prolonged infusional therapy allows for increased exposure of susceptible cells to the drug (Nicum et al., 2003). The side-effect profile with the prolonged infusional pattern differs, producing more hand-foot syndrome with decreased mucositis, diarrhea, and myelosuppression—side effects often seen with bolus administration. However, continuous infusion of 5-FU also has been shown to be superior to bolus 5-FU in terms of tumor response, achieving a slight increase in overall survival. Although the method of continuous infusion was statistically superior, oncologists in the United States originally favored bolus administration techniques (Hoff & Pazdur, 2004). They did so, in part, because of a belief that patient compliance would be improved with bolus administration and that the continuous infusional method was more difficult to achieve, requiring placement of vascular access devices and leading to potential increases in hospitalization costs (Hoff & Pazdur).

National Comprehensive Cancer Network and National Cancer Institute Adjuvant Therapy Guidelines

Guidelines that help healthcare providers make decisions regarding adjuvant therapy for colon cancer include the National Comprehensive Cancer Network (NCCN) guidelines, which provide specific recommendations for treatment of stage II and III colon cancer, and the National Cancer Institute (NCI) guidelines. The NCCN guidelines state that the administration of 5-FU and leucovorin, capecitabine, or 5-FU/leucovorin/oxaliplatin (FOLFOX or FLOX [bolus 5-FU, leucovorin, and oxaliplatin]) should be considered in stage IIA disease without high-risk features (T3, N0, M0) (NCCN, 2006).

For patients with T4 disease (stage IIB) with N0, M0, or T3 with localized perforation or close, indeterminate margins, as well as patients at high risk for systemic recurrence, such as those with grade 3 or 4 disease, lymphatic or vascular invasion, original presentation with bowel obstruction, or less than 12 lymph nodes examined, 5-FU and leucovorin, capecitabine, or 5-FU/leucovorin/oxaliplatin (FOLFOX or FLOX) should be the treatment choices (NCCN, 2006). All such patients should be considered for participation in a clinical trial, and the panel also recommended the option of “observation only” (NCCN, 2006).

The updated NCCN guidelines for stage III colon cancer (nodal involvement) recommend that all patients receive adjuvant therapy with 5-FU, leucovorin, and oxaliplatin or capecitabine or 5-FU and leucovorin. The treatment options include FOLFOX or FLOX (bolus 5-FU, leucovorin, and oxaliplatin), although diarrhea is significantly more prevalent with FLOX. The addition of radiation therapy is a consideration for T4 with penetration to a fixed structure. Irinotecan is not recommended in the adjuvant setting in the guidelines but is one of the recommended therapies for metastatic disease.

The NCI guidelines are somewhat more conservative and call for patients with stage III colon cancer to receive wide surgical resection and anastomosis, and patients not considered candidates for clinical trials should receive 5-FU and leucovorin for six months. Although the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial is discussed briefly in the guidelines as prolonging disease-free survival in patients receiving FOLFOX, the lack of positive overall survival data at the time of guideline development is noted, and the recommendation for chemotherapy options other than 5-FU and leucovorin is for patients on clinical trials (NCI, 2004).

Key Clinical Trials Leading to Changes in Adjuvant Therapy Options

For decades, 5-FU, at times in combination with leucovorin or levamisole, was the mainstay of treatment for patients with

1990: 5-fluorouracil (5-FU) with levamisole is found to be better than surgery alone.

1994: 5-FU with leucovorin is found to be better than surgery alone.

1998: 5-FU with leucovorin is found to be better than 5-FU with levamisole; treatment duration decreases to six months; monthly treatments are equivalent to weekly.

2002: Semimonthly 5-FU with leucovorin is equal to monthly bolus 5-FU and leucovorin.

2003: 5-FU with leucovorin plus oxaliplatin leads to a survival advantage in stage III.

2004: Bolus 5-FU with leucovorin plus irinotecan has no survival advantage in stage III; capecitabine is equivalent to 5-FU with leucovorin.

The future: Tailored therapies will be based on molecular and pathologic characteristics.

Figure 4. Chronology of Adjuvant Therapy for Colon Cancer

stage III colon cancer. Recently, several crucial clinical trials have reported results that have challenged providers to change the way they treat this patient population. The changes were incorporated in the NCCN guidelines for the management of colon cancer.

The Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer Trial

The MOSAIC trial results were reported in the *New England Journal of Medicine* (Andre et al., 2004). The goal of the trial was to challenge standard 5-FU and leucovorin as adjuvant therapy for colon cancer. The 1,123 participants had stage II or III colon cancer and were assigned randomly to receive either 5-FU and leucovorin or FOLFOX after surgical resection for a total of six months of therapy. The primary endpoint of the trial was disease-free survival, not overall survival (Andre et al.).

After a median follow-up of 37.9 months, 237 patients in the FOLFOX group had a cancer-related event, compared with 293 patients in the 5-FU and leucovorin group (21.1% versus 26.1%; $p = 0.002$). Disease-free survival at three-year analysis was 78.2% for the FOLFOX group versus 72.9% in the 5-FU and leucovorin group (Andre et al., 2004). The disease-free survival data were more significant for the patients with stage III disease compared with stage II, although benefit was derived for the higher-risk stage II patients in a subgroup analysis (Hickish et al., 2004). About 40% of the trial's patients had stage II disease, and the patients in the FOLFOX4 arm of MOSAIC had a reported 20% risk reduction for disease recurrence versus those randomized to the 5-FU and leucovorin arm (Hickish et al.). Further evaluation of the trial results and stratification of potential risk factors for stage II patients will help determine who will benefit most from adjuvant therapy in this population. The MOSAIC trial results were the basis for the changes in the 2005 NCCN guidelines.

The MOSAIC trial reported a statistically significant improvement in disease-free survival in the patients receiving FOLFOX compared with those in the 5-FU and leucovorin arm. The overall survival endpoint has been the emphasis of clinical oncology research; thus, the three-year disease-free survival endpoint of the MOSAIC trial generated some controversy (Grem, 2004). Disease-free survival is defined as the time from randomization to relapse of disease or death; overall survival is considered to be the period from randomization to death from any cause, which typically is observed over five years or longer (Andre & de Gramont, 2004). Because most colon cancer relapses occur in the first three years after surgery, some researchers believe that three-year disease-free survival is a valid endpoint for efficacy and a way of allowing clinical study results to be reported more quickly and, thus, incorporated into clinical practice and benefit patients sooner (Andre & de Gramont). A meta-analysis of 15 previous trials studying adjuvant therapy in more than 12,000 patients demonstrated that the three-year survival rate does serve as an accurate predictor of five-year overall survival (Sargent et al., 2004). The information led to the recommendation by the FDA Oncologic Drug Advisory Committee to accept the three-year marker for disease-free survival as the new endpoint for the approval of adjuvant therapies in colon cancer (Goetz & Grothey, 2004).

Cancer and Leukemia Group B Intergroup Trial C89803

Weekly bolus irinotecan plus 5-FU and leucovorin (IFL) compared with weekly 5-FU and leucovorin was evaluated as adjuvant therapy for stage III colon cancer in the Cancer and Leukemia Group B (CALGB) Intergroup Trial C89803. Results were presented in abstract form at the 2004 ASCO meeting (Saltz et al., 2004). The phase III study randomized 1,264 patients to receive either IFL or 5-FU and leucovorin. At the three year reporting, no improvement was noted with IFL over 5-FU and leucovorin alone, and the weekly protocol was associated with greater toxicity and an increased risk of early death (Saltz et al.). Although the incidence of grade 3 or 4 diarrhea generally was the same in the two treatment arms, the rates of neutropenia and febrile neutropenia were higher on the IFL regimen, with an increase in drug-related deaths (2.8% versus 1.1% in the 5-FU and leucovorin arm). The authors concluded that bolus IFL should not be used in the adjuvant setting (Saltz et al.).

Additional information on the use of irinotecan in the adjuvant setting for high-risk disease was reported at the ASCO 2005 meeting in abstract form for the French ACCORD-II trial, in which preliminary analysis showed no difference in event-free survival between the two arms (adjuvant 5-FU and leucovorin with irinotecan as compared to 5-FU and leucovorin), although important prognostic factors were unbalanced between the two arms (Ychou et al., 2005). The PETACC-III trial, also reported at ASCO in 2005, is an international trial that randomized 880 patients with stage II colon and intraperitoneal rectal cancers and 2,094 patients with stage III disease. Out of each group, half of the patients were treated with the standard fluorouracil-based regimen and the other half with standard therapy plus irinotecan. Irinotecan was found to increase efficacy of 5-FU and leucovorin in patients with stage III colon cancer, although without reaching statistical significance at a median follow-up of 32 months, and considerably increased the efficacy of 5-FU and leucovorin in the pooled population of stage II and III patients (Van Cutsem et al., 2005)

Xeloda in Adjuvant Colon Cancer Trial

Capecitabine is an oral fluoropyrimidine that is converted to the active form of 5-FU by thymidine phosphorylase (an enzyme that is found at much higher levels in tumor tissue versus healthy tissue in the body) (Reddy, 2004). The combination of capecitabine with oxaliplatin (also known as the XELOX regimen) was shown to be efficacious as first-line treatment for metastatic colon cancer, with response rates and overall survival similar to that of 5-FU, leucovorin, and oxaliplatin. The FDA recently approved capecitabine as a single-agent therapy in the treatment of colon cancer in the adjuvant setting (Reddy). Capecitabine originally was indicated as a first-line treatment of metastatic colon cancer; recent data from the Xeloda in Adjuvant Colon Cancer Trial have shown that capecitabine is as effective as bolus 5-FU and leucovorin in the adjuvant treatment of colon cancer (Scheithauer et al., 2003). The researchers randomized 1,987 patients with resected stage III colon cancer to oral capecitabine or bolus 5-FU plus leucovorin (via the Mayo Clinic regimen) over a period of 24 weeks (Twelves et al., 2005). The primary efficacy endpoint was equivalence in disease-free survival and

at the median follow-up of 3.8 years; capecitabine was at least as effective as the 5-FU bolus regimen, with a trend toward superiority in disease-free survival ($p = 0.0528$) and overall survival ($p = 0.0706$) (Cassidy et al., 2004). Subsequently, Twelves et al. reported that capecitabine improved relapse-free survival, and the patients on oral capecitabine therapy had significantly fewer adverse events than those receiving 5-FU and leucovorin. In the capecitabine arm, hand-foot syndrome was significantly higher and was managed with dose reduction. In the 5-FU and leucovorin arm, more patients had diarrhea, mucositis, nausea and vomiting, hair loss, myelosuppression, and infection (Cassidy et al.).

Of interest, the capecitabine arm generated considerable cost savings in mean resource use compared with the 5-FU and leucovorin arm. The costs were calculated by assessing the data on study drug administration, provider visits, and medications required for adverse events and included time spent on travel, clinic waits, and treatment administration time (Reddy, 2004). Measurement of additional nursing time required for instruction and reinforcement of patients taking oral therapy was not taken into account and could increase costs.

The MOSAIC trial results have challenged clinicians to re-evaluate standard adjuvant chemotherapy for colon cancer and to consider FOLFOX as the new standard for stage III patients requiring adjuvant treatment as well as for stage II patients with poorer prognostic factors. Although the overall survival in stage II patients is 70%–80% five years after surgery, for patients with high-risk stage II disease, the outcome drops to 40%–50% overall survival at five years, similar to stage III (Figueredo, Charette, Maroun, Brouwers, & Zuraw, 2004).

The Potential Role of Biologics

Two new agents approved in 2004 for metastatic colon cancer are from the biologic arena, and considerable interest exists in future studies of the antiangiogenesis and anti-epidermal growth factor agents combined with oxaliplatin and 5-FU in adjuvant therapy for patients with colon cancer, although the FDA has not approved biologics in this setting. Cetuximab is a monoclonal antibody that specifically targets the epidermal growth factor receptor; bevacizumab is a monoclonal antibody that has activity against the vascular endothelial growth factor (VEGF) (Wilkes, 2005). Cetuximab affects signaling from the growth factor, thereby reducing cell proliferation (Wilkes & Barton-Burke, 2005). Bevacizumab specifically targets VEGF, thereby affecting blood supply to a tumor itself, with the goal of reducing tumor growth (Wilkes). The FDA has approved bevacizumab given every two weeks in combination with a 5-FU regimen for the first-line treatment of metastatic colon cancer and cetuximab weekly as a single agent or in combination with irinotecan as second-line therapy for metastatic colon cancer (Wilkes).

Although bevacizumab and cetuximab can add significantly to the overall cost of metastatic therapy for colon cancer, bevacizumab has been shown to prolong median survival from 15.6 to 20.3 months when added to standard IFL therapy in patients with metastatic colon cancer, and cetuximab improved time to progression from 1.5 to 4.5 months in combination therapy (Viale, Fung, & Zitella, 2005). Studies are under way to investigate FOLFOX plus bevacizumab as first-line therapy in advanced colon cancer (the Intergroup S303 trial) and in adjuvant therapy, with the National Surgical Adjuvant Breast

and Bowel Project C-08 trial looking at stage II and III colon cancers and an Eastern Cooperative Oncology Group trial looking at high-risk stage II patients (Andre & de Gramont, 2004; O'Connell, 2004). Potential advances in the adjuvant therapy of patients with colon cancer can help a significant number of patients because colon cancer is such a common disease; therefore, pursuing improvements in the adjuvant setting is worthwhile. Additionally, the cost of therapy rises as more patients are treated with chemotherapy in the adjuvant and metastatic settings; further study of genomic markers in colon cancer may help to define the populations of patients who may benefit most from therapy (Allen & Johnston, 2005). Predictive markers may assist clinicians in determining patient responses to specific agents. Microsatellite instability (MSI) also is common in colon cancer, and patients with MSI-high phenotype have shown improved survival from stage II and stage III colon cancer as well as better recurrence-free survival; adjuvant therapy did not benefit the patients (Allen & Johnston).

Special Considerations for Older Patients

Colon cancer is primarily a disease of older people. Older patients often are described in studies as those more than 65 years of age, and 60% of neoplasms occur in patients in that age group (Sargent et al., 2001). Older patients have special learning needs to successfully receive chemotherapy. Published guidelines specifically call for more careful monitoring and interventions for patients older than 70 years of age (NCCN, 2005).

Unfortunately, as older patients are diagnosed with colon cancer, their chances of receiving chemotherapy may decrease. One study reported the prevalence of chemotherapy decreasing progressively, from 73% among patients aged 65–69 years to 9% for patients older than 85 years (Sundararajan, Grann, Jacobson, Ahsan, & Neugut, 2001). Interestingly, patients with colon cancer aged 70 and older who received 5-FU-based chemotherapy derived benefits similar to those of their younger counterparts without significant increases in toxic effects. Therefore, older patients should be considered for appropriate therapy based on disease and not age (Andre & de Gramont, 2004; Arora & Potter, 2003; Sargent et al., 2001). One analysis of adjuvant chemotherapy found it to be beneficial in patients with resected stage II and III colon cancer, with older patients showing no increase in nausea, vomiting, stomatitis, or diarrhea compared with younger patients, although the incidence of leukopenia was higher in the patients receiving 5-FU (Arora & Potter). When surveyed, older patients indicated that they were just as likely to want chemotherapy as younger patients, although they were less likely to trade significant toxicity for added survival. The patients also indicated that the most likely determinant in their decisions to pursue treatment was their physicians' advice (Schrag, Cramer, Bach, & Begg, 2001). Because older patients may have life expectancies into their 80s or 90s, oncology nurses and healthcare professionals need to make sure that they have the opportunity to make appropriate therapy decisions (Schrag et al.).

Implications for Nurses

As the public becomes aware of new research findings, oncology nurses may encounter patients who have questions regarding possible new options in therapy and should be

prepared to discuss the choices. Additionally, research has shown that despite national guidelines recommending adjuvant chemotherapy for stage III and IV colon cancer, only 45%–55% of such patients actually receive the treatment (Oliveria, Yood, Campbell, Yood, & Stang, 2004). Although patient refusal accounted for some of the disparity, many patients were not referred to an oncologist for treatment. Reasons most commonly given for lack of referral included patient comorbidities; significant predictors of receiving an oncology referral or visit were younger age (younger than 70 years) and stage III disease at diagnosis (Oliveria et al.).

Oncology nurses can play an important role in helping to identify appropriate patients for adjuvant therapy. Education of patients and healthcare providers regarding the national guidelines and patient selection is essential. Adjuvant therapy for colon cancer can improve survival for patients by reducing mortality by as much as 30%, and the rate may improve further with the addition of newer adjuvant therapies (Meyerhardt & Mayer, 2005). Healthcare providers must refer appropriate patients to an oncologist, discuss treatment options with patients, and provide accurate information on statistical chances of recurrence if treatment is not initiated. Discussion should occur regarding potential side effects of therapy; decisions regarding appropriate therapies may be dependent on toxicities of individual chemotherapy treatments.

Adjuvant Therapy Drug Toxicities

Nurses who care for patients with cancer are skilled in the administration of chemotherapy agents for colon cancer. The common side effects associated with bolus 5-FU and leucovorin are mucositis, diarrhea, and myelosuppression; when the drugs are given as a continuous infusion, the side-effect profile differs, favoring an increase in hand-foot syndrome (Coyle & Wenhold, 2001) (see Figure 5). Protracted infusion of 5-FU and capecitabine (as a prodrug for 5-FU) are associated with a higher incidence of hand-foot syndrome, which manifests in tingling, erythema, and tenderness of the palms of the hands or soles of the feet (Timmerman, 2001; Wilkes, 2005). If therapy is not interrupted, the symptom complex can progress to swelling, pain, blisters, and ultimately desquamation (Wilkes). Nurses should be competent in the assessment and management of hand-foot syndrome (also known as palmar-plantar erythrodysesthesia). Patients' timely reporting of symptoms to healthcare providers can help to identify the complication earlier, leading to prompt intervention (see Figure 6). Capecitabine is an orally administered therapy; therefore, nurses must have a means for communication to patients in the homecare setting, where symptoms may occur unnoticed by healthcare personnel.



Figure 5. Hand-Foot Syndrome

Note. Photos courtesy of Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP. Reprinted with permission.

Signs and Symptoms

Painful erythema of the hands and feet; may be preceded by paresthesia; can also present as swelling, desquamation, and blistering, possibly leading to moist desquamation or ulceration of the hands and feet

Pharmacologic Management

Systemic corticosteroids, pyridoxine, and topical 99% dimethylsulfoxide have been used with varying outcomes.

Nonpharmacologic Management

Topical wound care, elevation of the affected extremities, and cool compresses may provide symptom relief.

Figure 6. Assessment and Management of Hand-Foot Syndrome

Note. Based on information from Nagore et al., 2000; Roche Pharmaceuticals, n.d.

Oxaliplatin, as a third-generation cisplatin analog, has a different side effect profile, including neurotoxicity, nausea and hypersensitivity (which may present as a delayed reaction) (Viale et al., 2005). Oxaliplatin should be administered using dextrose-containing solutions and is considered mildly emetogenic (Sorich, Taubes, Wagner, & Hochster, 2004). Allergic reactions may occur in fewer than 10% of patients, and although they may be immediate with infusion, delayed responses also have been reported (Sorich et al.). The dose-limiting side effect of oxaliplatin is neurotoxicity, which occurs with increasing frequency after multiple cycles; patients should be assessed regularly for signs and symptoms of worsening neurotoxicity (see Table 2). Patients often present with peripheral neuropathy with dysesthesia in a stocking-glove distribution (Sorich et al.). One clinical case report suggested that venlafaxine (50 mg) helped to ameliorate some of the neurotoxic effects associated with oxaliplatin (Durand, Brezault, & Goldwasser, 2003). In a retrospective review of 161 patients, calcium-magnesium (1 g) infusions seemed to reduce the incidence and severity of acute oxaliplatin-induced symptoms (Gamelin et al., 2004). In the MOSAIC trial, grade 3 or 4 sensory neurotoxicity affected 12.4% of patients overall; however, the neurotoxicity was reversible in the majority of patients (Andre et al., 2004). Grade 3 or 4 toxicity at 18-month follow-up was 0.5%.

Cold can induce a sensory pharyngolaryngeal dysesthesia in about 10% of patients receiving oxaliplatin (Sorich et al., 2004). Administering the drug at room temperature and providing a warm beverage for an affected patient may minimize the side effects. Encouraging protection against cold exposure for five to seven days after drug administration also may help to reduce the occurrence of cold-induced dysesthesia (Sorich et al.).

Oncology nurses also should note that, although oxaliplatin is not officially classified as a vesicant, it can produce tissue necrosis; care should be taken with peripheral administration of the drug.

Special Considerations in Patient Education

Protracted infusion of 5-FU requires the placement of a vascular access device to facilitate the most frequently used 22-hour infusion time. Selection of the most appropriate device for each patient and patient instruction are needed. Patient education is crucial regarding central catheter choices and infusion management in the home setting. If home care cannot be obtained to help a patient manage the infusion or if

Table 2. National Cancer Institute Common Terminology Criteria (Version 3.0) Neurosensory Toxicity Scale

Grade	Criteria
One	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) that does not interfere with function
Two	Sensory alteration or paresthesia (including tingling), interfering with function but not interfering with activities of daily living
Three	Sensory alteration or paresthesia, interfering with activities of daily living
Four	Disabling
Five	Death

Note. Based on information from National Cancer Institute, 2003.

the patient or caregiver cannot reliably care for the device and pump, the infusion may be conducted in the hospital setting, where nursing staff can monitor the longer infusion and assess for treatment-related side effects. However, hospitalization adds considerably to the cost of therapy.

Patient education regarding assessment and appropriate intervention for management of diarrhea is essential, and oncology nurses are in an ideal position to teach the importance of proper management (Wilkes, 2005). Guidelines regarding management of diarrhea have been updated to call for recognition of the early warning signs of complicated cases of diarrhea and the need for early and aggressive management, including antibiotic therapy (Benson, Ajani, et al., 2004).

Neurotoxicity in patients receiving oxaliplatin needs to be graded and assessed with each administration to determine progression of symptoms. Patients must be educated to report changes in sensation and functional skills to accurately assess the level of impairment from the potential neurotoxic effects of

oxaliplatin. Capecitabine, as an oral treatment, presents the need for adequate patient teaching regarding the signs and symptoms of hand-foot syndrome as well as promoting self-care activities that may help with the complication, such as cooling hands and feet to reduce blood flow, elevating hands and feet, and avoiding rubber gloves. Additionally, patients should remember to wear loose-fitting clothing and shoes, wear sun protection, and apply skin creams regularly (Roche Pharmaceuticals, n.d.). Reinforcement of reportable symptoms by nurses at the start of therapy is crucial because symptoms are likely to occur when patients are taking their therapy at home.

Conclusion

The management of colon cancer has seen remarkable advances; the FDA approval of oxaliplatin in the adjuvant setting for colon cancer is changing the way providers treat patients. Capecitabine has been approved in the adjuvant setting as well. More information about irinotecan, as well as biologic agents in the adjuvant setting, will become available as ongoing trials provide more data. Future directions in therapy may be guided by additional information regarding predictive markers in colon cancer. Data will help to individualize therapy for the common disease, continuing to add to clinicians' knowledge and improve survival for patients with colon cancer. Earlier (adjuvant) and more effective therapies will offer patients hope and a chance at long-term cure. Chemotherapy options for patients with colon cancer have expanded, and oncology nurses must be aware of appropriate therapy, recent research advances, and the specialized knowledge that is needed to administer the treatments safely, as well as to keep patients informed of the most current therapeutic options.

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