New Therapeutic Options in Colon Cancer: Focus on Oxaliplatin

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Colon cancer is the third leading cause of cancer death in the United States and the second leading cause in the Northern, Central, and Southern Americas. Appropriate treatment depends on the stage of malignancy, which is determined using the tumor-lymph node-metastases system. In stage III disease, adjuvant chemotherapy increases disease-free and long-term survival following surgery, and chemotherapy is the mainstay of treatment for advanced disease. New therapies are being evaluated, including oxaliplatin, a third-generation platinum analogue approved as first- and second-line therapy for metastatic colorectal cancer in Europe; the drug shows great promise combined with 5-fluorouracil/leucovorin or with irinotecan. The dose-limiting toxicity of oxaliplatin is neurologic, which can be acute or chronic; this can be prevented or reduced in some cases through patient education. Nurses play a critical role in education concerning prevention and management of oxaliplatin-related side effects.

Treatment Strategies

Treatment depends on the stage of the malignancy. Once a benign polyp transforms into a malignant lesion, surgical resection of the lesion with tumor-free margins is the optimal therapy (Skibber, Minsky, & Hoff, 2001). Ninety-five percent of colon cancers are adenocarcinomas, as they arise from the glandular epithelium of the colon. Prior to surgery, a computerized tomography scan and blood tests are performed to determine whether the tumor has spread beyond the colon to the liver or other organs. During surgery, lymph nodes adjacent to the colon are removed and tested to ascertain whether tumors are present. Following surgery, the tumor is staged to determine optimal therapy. Duke’s staging system, commonly used in the past, has been replaced by the tumor-lymph node-metastases (TNM) staging system (Sobin & Wittekind, 1997).

In stage III disease (i.e., when lymph nodes are involved), adjuvant chemotherapy clearly increases disease-free and long-term survival following surgery (Skibber et al., 2001). Whether adjuvant chemotherapy improves survival in stage II is unclear; as a result, clinical trials currently are being conducted to determine this. However, chemotherapy is recommended if a tumor is obstructive or has perforated the bowel wall (Benson et al., 2000). In advanced disease (i.e., stage IV), aggressive therapy may be considered for some conditions (e.g., hepatic resection for isolated liver metastases [Berg & Lilienfeld, 2000]); however, chemotherapy has remained the mainstay of therapy for advanced colon cancer. Currently, combination therapy with 5-fluorouracil (5-FU), leucovorin, and irinotecan represents the first-line therapy for metastatic colorectal cancer. This combination of drugs results in an overall response rate of 39.4% and survival of 14.8 months, which is significantly greater than with either irinotecan or 5-FU/leucovorin alone (Saltz, Locker, Pirotta, Elfring, & Miller, 1999). In one study, patients with metastatic colorectal cancer were randomized to receive irinotecan and supportive care or supportive care alone. Of those receiving irinotecan and supportive care, 36.2% survived one year versus 13.8% of those receiving supportive care alone (Cunningham et al., 1998).

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In an effort to increase response and survival, many new agents are being studied, including oxaliplatin. The National Surgical Adjuvant Breast and Bowel Project (NSABP, 2000) is conducting a national study comparing 5-FU, leucovorin, and oxaliplatin to 5-FU and leucovorin alone in patients with stage II or III colon cancer (NSABP C-07). The National Cancer Institute is conducting a study in the United States and Canada evaluating irinotecan and oxaliplatin, in combination and with other drugs, as initial therapy for advanced colorectal cancer. Oxaliplatin was approved in Europe as first- and second-line therapy for metastatic colorectal cancer and had response rates as a single agent of 10%–18% (Pazdur, 1998). Combining 5-FU and leucovorin yielded response rates of 7%–55% in previously treated patients and 29%–53% in chemotherapy-naïve patients (Giacchetti et al., 2000). In addition, 24%–44% of patients achieved disease stabilization when oxaliplatin was given as a single agent; 20%–71% achieved stabilization when they received oxaliplatin in combination with 5-FU and leucovorin (Cvitkovic & Bekradda, 1999).

**Oxaliplatin**

Oxaliplatin is a third-generation platinum analogue, manufactured as Eloxatin® (Sanofi-Synthelabo, New York, NY). As a member of the platinum family, oxaliplatin acts as an alkylating agent, forms cross-links among DNA strands in the cancer cell nucleus, prevents cancer-cell DNA from completing replication and transcription, and leads to cell death (Wilkes, Ingwersen, & Barton-Burke, 2002).

Currently, patients can receive oxaliplatin by participating in clinical trials, such as those described previously, or on a compassionate-use basis. The drug is given as a single agent or in combination with 5-FU and leucovorin at a dose of 85 mg/m² IV every two weeks or 130 mg/m² IV every three weeks. Oxaliplatin is infused via IV over a period of one or more hours. The combination of oxaliplatin and 5-FU produces a synergistic effect, and the 5-FU dose may need to be decreased accordingly (Berg & Lilienfeld, 2000). Oxaliplatin is incompatible with sodium chloride and therefore must be diluted in dextrose and water only. Contact with aluminum equipment (e.g., needles) must be avoided as aluminum degrades oxaliplatin. Because oxaliplatin also is incompatible with alkaline solutions, such as 5-FU, when the agents are administered in combination, oxaliplatin should be infused first and the line should be flushed well between solutions (Sanofi-Synthelabo, 2001).

### FIGURE 1. COLD DYSESTHESIA: SELF-CARE STRATEGIES FOR THE FIRST FIVE DAYS FOLLOWING OXALIPLATIN TREATMENT

- Avoid going outside in cold weather if possible; when it is absolutely necessary, wear warm mittens (rather than gloves), socks, and footwear.
- Have someone else warm up the car ahead of time, especially when you are getting into the car from home or after treatment.
- Try not to breathe deeply when exposed to cold air, such as winter cold or from an open refrigerator or freezer.
- Wear gloves when opening and reaching into a refrigerator or freezer.
- Avoid drinking coffee or tea and eating ice cream or other frozen desserts.
- Use a straw when drinking fluids.
- Avoid sucking ice chips during treatment.
- In hot weather, do not run an air conditioner at a high level in the house or car.
- Tell your nurse or doctor right away if you feel discomfort or tightness in the back of your throat or if you feel like you are having trouble breathing or swallowing. This sensation will go away in a few minutes. Try to relax and think of something very pleasant outside of your present situation. Your doctor or nurse also may give you something to help you relax.

With the patient’s eyes closed, compare one side of the body to the other.

**Pain:** Using broken end of a cotton swab, test distally to proximally (e.g., fingers, hand, forearm; toes, feet, legs) and ask the patient to indicate when he or she feels pain.

**Light touch:** Using cotton end of swab, test distally to proximally (e.g., fingers, hand, forearm; toes, feet, legs) and ask the patient to indicate when he or she feels a touch.

**Position:** Grasping the last joint of the patient’s index finger from the side, move the joint up or down and ask the patient whether the finger is pointing up or down. Repeat this on the opposite side, as well as with each of the big toes. Compare side to side. If position sense is impaired, move on to the next proximal joint (e.g., wrist, ankle).

**Vibration:** Test both sides of the body using a tuning fork. Tap the tuning fork on the heel of your hand to begin vibration, then place the rounded end on the interphalangeal joint of the patient’s middle finger. If the patient senses pressure, ask him or her to tell you when the sensation stops, and touch the hammer to gently strike the tendon. If the vibration is difficult to elicit, have the patient interlace the fingers of both hands and try to pull them apart as you test the reflex. Response is graded on a scale of 0–4+ as follows.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>No response, often abnormal</td>
</tr>
<tr>
<td>1+</td>
<td>Slightly diminished, may be normal</td>
</tr>
<tr>
<td>2+</td>
<td>Normal</td>
</tr>
<tr>
<td>3+</td>
<td>Brisk, but may not be related to disease</td>
</tr>
<tr>
<td>4+</td>
<td>Very brisk, hyperactive, abnormal</td>
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**Achilles reflex:** Foot should plantar flex. If an abnormality is present, it may reflect a problem at nerves S-1 and S-2 of spinal cord.

**Quadriceps reflex:** Elicits knee jerk, which should extend the leg; tests nerves L-3 and L-4.

**Biceps reflex:** The elbow should flex; tests nerves C-5 and C-6.

**Triceps reflex:** The elbow should extend; tests nerves C-7 and C-8.

### FIGURE 2. SYSTEMATIC ASSESSMENT OF DYSESTHESIA AND PERIPHERAL NEUROPATHY: ASSESSMENT OF SENSORY FUNCTION

*Note.* Based on information from Wilkes, 1999.
Muscle strength: Test by having the patient resist your movement as you assess hand grip, shoulder strength, biceps/triceps, hip flexion, plantar flexion, and dorsiflexion. Muscle strength is graded on a scale from 0–5 (Bates, 1995).

0 = no muscular contraction noted
1 = barely detected, flicker of contraction
2 = unable to hold muscle against gravity
3 = active movement against gravity
4 = active movement against gravity and against some resistance
5 = active movement against full resistance without evidence of fatigue (normal)

Coordination: Assess gait, observing the patient as he or she walks for evidence of hesitation, stumbling, or holding on to walls.

**Figure 3. Assessment of Motor Function**

*Note. Based on information from Wilkes, 1999.*

The dose-limiting toxicity of oxaliplatin is neurologic, which can be acute or chronic, and is manifested by peripheral neuropathy. Other toxicities include mild bone marrow suppression, which is increased when oxaliplatin is combined with 5-FU and leucovorin; this results in mild neutropenia and thrombocytopenia. Nausea, vomiting, and diarrhea, which can be severe, are common side effects. Occasional allergic reactions have been observed, including itching, hives, flushing, skin rashes, fever, and chills. How-ever, severe anaphylactic reactions can occur in rare cases (Hochster et al., 2000). In less than 0.1% of patients studied, transient vi-
sion loss and interstitial lung disease have been found, which warrants drug discontinu-
ance if unexplained pulmonary symptoms, such as nonproductive cough, dyspnea, crackles, or the presence of pulmonary infiltrates on chest x-rays, occur (Sanofi-Synthelabo, 2001). When administered in combination with 5-FU and leucovorin, potential side effects include stomatitis and pharyngitis, and less commonly, alopecia, fever, fatigue, malaise, increased hepatic en-
zymes, and hand-foot syndrome (Pazdur, 1998).

**Neurotoxicity**

Acute oxaliplatin-induced neurotoxicity is sensory, occurs early in treatment, and is un-
usual in its presentation. Occurring later in treatment, chronic neurotoxicity is similar to that seen with cisplatin, and although its pri-
mary manifestation is sensory, chronic neu-
rotoxicity can become sensorimotor if allowed to progress (Haller, 2000). Acute neurotoxic-
ity is common, affecting up to 90% of pa-

tients, and is characterized by symptoms precipitated by exposure to cold during or up to five days following drug infusion (Sanofi-Synthelabo, 2001). The symptoms are mild and include dysesthesia and paresthesia, which affect the buccal and pharyngolaryngeal areas and distal extremities. For example, a pa-
tient may complain of numbness and tingling of the fingertips when reaching into the freezer

or associated with cold, chills, or inhalation of very cold air either during infusion or on the way home after treatment. Laryngopharyngeal dysesthesia resolves on its own, usually within minutes. Pa-

tients often find this experience frightening, but it does not impair respiration or oxygen-

ation, as shown by oxygen saturation values compared to baseline. In these situations, ben-

zodiazepines (i.e., diazepam) have been given to treat the associated anxiety, and the phe-


nomenon did not recur with subsequent oxaliplatin treatments (G. Quilon, personal communication, January 21, 2000).

In some cases, patients may complain of muscle cramping, often associated with cold, in areas such as the hand or forearm. When this occurs, the hand may remain involuntarily clenched for a short time, but the problem re-
solves spontaneously (Ptacek, 1998). Re-

search is ongoing to more clearly define this occurrence. In some reports, this cramping appears to resemble myotonia, a condition that prevents a muscle from relaxing completely after voluntary contraction (Ptacek).

Nurses must educate their patients about the possibility of these symptoms and explain preventive measures. Figure 1 presents im-
portant points for patient education. Figures 2 and 3 describe a systematic assessment. Two toxicity scales showing grading systems are shown in Table 1 and Figure 4. A stan-

dardized care plan for the patient receiving oxaliplatin, with emphasis on potential for neurotoxicity (including acute and peripheral neuropathy), is shown in Table 2.

A more chronic neurotoxicity that is asso-

ociated with cisplatin treatment can occur. Al-

though it is less common following oxaliplatin than following cisplatin, moderate peripheral neuropathy occurs in about 10%–15% of patients after a cumulative dose of 780–850 mg/m² of oxaliplatin has been received (Berg & Lilienfeld, 2000).

Peripheral neuropathy is primarily sen-

sory. It begins with paresthesia (i.e., “pins and needles” sensation or burning pain) and numbness in a stocking-glove distribution, affecting the fingertips and toes first and
### Table 2. Standardized Nursing Care Plan for Patients Receiving Oxaliplatin

<table>
<thead>
<tr>
<th>Nursing Diagnosis</th>
<th>Nursing Plan</th>
<th>Expected Outcomes</th>
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| Potential for sensory perceptual alterations related to laryngopharyngeal dysesthesia | - Teach the patient that this may occur.  
- Teach the patient the preventive measures outlined in Figure 1.  
- If the symptom develops, discuss anxiolytics prior to next therapy. | - Laryngopharyngeal dysesthesia will be prevented.  
- If laryngopharyngeal dysesthesia occurs, the patient will tolerate the experience safely. |
| Potential for injury related to peripheral neuropathy (e.g., decreased sensitivity to temperature, gait disturbance, decreased proprioception) | - Assess the integrity of sensory function, especially proprioception and vibration, and temperature and pain.  
  - Sensory perception to light touch, pin prick, vibration, positioning, temperature  
  - Patient’s ability to tolerate light touch, cool water, presence of numbness or tingling, and presence of painful sensations  
  - Proprioception testing of station, gait, deep tendon reflexes, muscle weakness or atrophy, and balance  
  - Ability to sense placement of body parts, ability to write, and evidence of muscle weakness  
  - Effect of any symptoms or changes in comfort or ability to do activities of daily living (ADLs) or other activities important to patient. | - The patient will not experience injury.  
- The patient will report changes in tactile and proprioceptive function.  
- The patient will develop self-care measures that ensure safety. |
| Potential for impaired self-care related to peripheral neuropathy: Tactile and proprioception problems | - Assess the patient’s ability to perform ADLs, such as holding a fork, cutting food, maintaining good hygiene, dressing, walking, and handwriting.  
- With patient, discuss and develop strategies to meet self-care needs.  
  - Refer to occupational therapy as needed for splint, etc.  
  - Involve family members in care planning as permitted by patient.  
  - Involve resources as needed (e.g., visiting nurse, homemaker, home health aides). | - The patient will identify activities of self-care that are inadequate or difficult.  
- The patient will identify strategies to meet his or her needs. |
| Altered comfort level potential related to painful paresthesia | - Assess the patient’s comfort level and for the presence of severe tingling, numbness, burning, or other sensations.  
- Assess the quality, intensity, and frequency of discomfort.  
- Identify precipitating factors, such as warm or cold stimulation, and help the patient develop a realistic plan to avoid triggers.  
- Discuss analgesics with physician (e.g., gabapentin for systemic therapy, local treatment such as application of EMLA® cream [lidocaine/prilocaine, AstraZeneca, Wilmington, DE]).  
- Consider nonpharmacologic interventions, such as guided imagery, progressive muscle relaxation, or massage, if they are acceptable and available. | - The patient will have decreased pain. |
| Impaired mobility related to peripheral neuropathy: Decreased proprioception, muscle dysfunction | - Assess the patient’s level of activity, muscle strength, and level of mobility at baseline prior to chemotherapy, prior to each treatment, and at each visit once therapy is completed.  
- Encourage the patient to use visual cues to determine the position of body parts if proprioception is impaired.  
- Teach measures to prevent injury.  
- Refer for physical or occupational therapy for assistive devices as needed. | - The patient will ambulate safely. |
| Potential for sexual dysfunction related to peripheral neuropathy: Altered tactile sensation, muscle weakness, changes in role | - Discuss the impact of treatment-related dysfunction on ability to give and receive affection, sexuality, social role, and self-esteem with the patient.  
- Discuss appropriate alternative means of sexual expression and provide emotional support.  
- Refer for specific sexual counseling as needed. | - The patient and his or her partner will identify effects on sexual expression.  
- The patient and his or her partner will identify alternative methods of sexual expression. |

*(Continued on next page)*
Potential for role change (self-concept, self-esteem, social function, occupational role) related to peripheral neuropathy disability

- Assess the impact of sensory or perceptual dysfunction on social and work roles and the ability to meet role expectations of self and family.
- Discuss modifications in job and role, as appropriate and available.
- Refer the patient to occupational or physical therapist for evaluation concerning assistive devices to promote rehabilitation.
- Encourage independence where possible and provide positive reinforcement for accomplishments. Encourage the patient to accept assistance from family and friends in areas where dependent.
- Provide emotional support during grief reaction, and assess the need for support or counseling.
- Provide information about support groups and other resources to promote effective coping.

Knowledge deficit related to possible progression of peripheral neuropathy

- Teach the patient about potential side effects of neuropathy and how to report them.
  - Pins-and-needles sensation in hands or feet, or choking sensation in throat when exposed to cold
  - Numbness and tingling in hands or feet during or after therapy
  - Change in gait, such as tripping or stumbling
  - Weakness in muscles
  - Inability to perform fine motor movement, such as buttoning a shirt or picking up a coin from a flat surface
  - Change in sexual functioning.

Potential for infection and bleeding related to mild neutropenia and thrombocytopenia

- Assess white blood cell count, absolute neutrophil count, and platelet count prior to each treatment and discuss abnormalities with the physician.
- Teach the patient to report temperatures more than 100.5° F and signs of infection, such as productive cough and dysuria, immediately.
- Teach the patient to report bleeding, such as bleeding gums after brushing teeth, immediately.
- Teach the patient self-care measures to minimize infection and bleeding (e.g., washing hands, avoiding crowds or people with infections, keeping skin and mucous membranes intact, performing systematic oral hygiene, gentle cleansing of teeth, preventing constipation).

Potential alteration in nutrition related to nausea and vomiting

- Discuss aggressive antiemetic regimens to prevent nausea and vomiting with initial treatment, especially when the drug is given in combination.
- Teach the patient to self-administer an antiemetic for the first 24 hours after treatment as directed.
- Teach the patient to report nausea or vomiting not controlled by antiemetics.
- Teach the patient to drink two to three liters of fluid per day, as tolerated.
- Teach the patient nonpharmacologic measures, such as guided imagery and relaxation exercises, as appropriate and available.

Potential alteration in elimination or diarrhea

- Teach the patient that this may occur and to take usual antidiarrheal medicine, such as loperamide. Teach the patient to avoid taking laxatives.
- Teach the patient to notify his or her healthcare provider if diarrhea occurs and does not resolve with antidiarrheal medicine.
- Teach the patient to consume two to three liters of fluid (especially sports drinks and soups) per day.
- Teach the patient dietary modifications, such as the BRAT (bananas, rice, applesauce, and toast) diet, and instruct the patient to increase cheese intake.
- Teach the patient local skin care of the rectum to promote comfort if diarrhea occurs.
Potential for injury related to allergic reaction

- Teach the patient to report rashes, itching, shortness of breath, dizziness, and new symptoms immediately.
- Assess the patient’s history of allergies, including any allergy to platinum.
- Assess baseline vital signs prior to initial treatment and each subsequent treatment. Assess more frequently if any abnormalities are found or if the patient develops any untoward effect.
- Stop the drug, ensure that the patient has a patent airway, and notify the physician immediately if an allergic reaction occurs. Discuss further management with the physician.
- Keep emergency equipment in the treatment area.

Expected Outcomes

- Allergic reactions will be identified and managed early.

Potential alteration in oxygenation related to rare pulmonary toxicity

- Teach the patient to report any changes in usual respiratory function, such as shortness of breath or cough.
- Assess baseline pulmonary function, such as breath sounds, respiratory rate, and oxygen saturation on room air, and assess prior to each treatment.
- Discuss any changes in pulmonary function with the physician and anticipate further diagnostic studies, such as a chest x-ray and pulmonary function studies.

Expected Outcomes

- Pulmonary toxicity will be identified early and managed.

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then progressing proximally to the hands and feet. Symptoms may diminish between cycles of treatment, but they last longer with each subsequent treatment. Although symptoms usually resolve in four to six months, the neuropathy may progress to motor dysfunction with functional impairment if treatment continues (Henderson, 1998).

If large fiber nerves are affected by oxaliplatin, the neurotoxicity will impair vibration and position sense. This sense is critical to coordinated movement because it regulates the body’s sense of spatial position. Patients with this impairment are at risk of injury from falls and may have difficulty with activities of daily living and self-care. This may necessitate referral to physical or occupational therapists for exercises and self-help equipment, as well as to home-health services.

Temperature and pain sensation become altered if small nerve fibers are affected. Patients with temperature insensitivity are at risk for thermal injury and should be advised to lower the temperature on their water heaters or have someone test the water before doing dishes, bathing, or washing hands.

Several agents have been studied to manage the neuropathy caused by oxaliplatin, especially D-aspartate antagonists, including some anticonvulsants and other investigational agents (Baron, 2000). In addition, agents that deplete substance P, such as capsaicin cream (Ellison et al., 1997), and preparations, such as eutectic mixture of local anesthetics cream (EMLA®, lidocaine/prilocaine AstraZeneca, Wilmington, DE) (Fassoulaki, Saramtopoulos, Melemeni, & Hogan, 2000), or topical lidocaine (Devers & Galer, 2000) may provide local comfort. In a small study (N = 15) by Mariani et al. (2000), gabapentin offered complete relief of neuropathic symptoms in patients receiving oxaliplatin; when gabapentin treatment ceased, symptoms returned, but they resolved with the resumption of treatment.

Nurses systematically must assess for signs or symptoms of neurotoxicity, especially with peripheral neuropathy, so any progression can be identified early. Some early symptoms include the inability to pick up a small object (e.g., a coin from a flat surface) or button a shirt. In rare cases, patients may exhibit Lhermitte’s sign, in which flexion of the neck causes an electric shock-like sensation through the back and neck; this is indicative of secondary degeneration of the posterior column (Taieb, Freyer, Rambaud, Decos, & Trillet-Lenoir, 2000). If symptoms of peripheral neuropathy are present, nurses must assess the impact of these symptoms on the patients’ safety and quality of life.

Summary

Clinical trials currently underway will help identify the place oxaliplatin will hold in the management of patients with advanced colon cancer. In the meantime, however, nurses must understand this agent—not only its promise, but its potential side effects and important points in patient care and education. Oxaliplatin is unusual in its potential side effects of laryngopharyngeal dysesthesia and other cold-induced problems. Nurses play a critical role in explaining these possible side effects to patients and in helping them understand the importance of avoiding cold exposure. Oxaliplatin is an agent that shows great promise in the treatment of advanced colon cancer when administered in combination with 5-FU and leucovorin or with irinotecan.

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References


For more information on this topic, visit the following Web sites:

Colon Cancer Alliance www.ccalliance.org

Colon Cancer News www.coloncancerweek.org

CancerNet: Colon and Rectal Cancer www.cancernet.nci.nih.gov/wyntk_pubs/colon.htm

These Web sites are provided for information only. Hosts are responsible for their own content and availability. Links can be found using ONS Online at www.ons.org.