Hypersensitivity Reactions to Oxaliplatin: What Nurses Need to Know

Kathleen Bonosky, RN, BSN, OCN®, and Rickey Miller, PharmD, BCOP

Colorectal cancer (CRC) is the third-leading cause of cancer death in the United States. With the advent of new chemotherapy drugs, such as oxaliplatin, for CRC, disease-free and long-term survival has improved in this patient population. As oxaliplatin use increases, more hypersensitivity reactions may be expected. The etiology of these reactions is unclear but may be a combination of immunologic responses. Pretreatment, treatment, and desensitization protocols are available to prevent and treat hypersensitivity reactions. Nurses’ rapid assessment and management of infusion-related hypersensitivity reactions are vital to ensuring the safe administration of oxaliplatin.

Colorectal Cancer and Treatment

CRC is the third most common cancer in men and women, accounting for 11% of all newly diagnosed cancers and 57,100 deaths annually in the United States (American Cancer Society [ACS], 2005). ACS estimates that in 2005 about 145,290 people will be diagnosed with CRC and 56,290 will die as a result of the disease. Only 37% of CRC cases are discovered in the early stage, when the disease is asymptomatic; most patients are diagnosed at later stages and present with symptoms of rectal bleeding, abdominal pain, and/or changes in bowel habits. The primary risk factor for CRC is age, with more than 90% of cases diagnosed in individuals older than age 50 (ACS). Other risk factors include a family history of CRC, polyps, familial syndromes (i.e., hereditary polyposis), or inflammatory bowel disease. Early-detection recommendations by ACS include annual fecal occult blood testing or sigmoidoscopy every five years after age 50. Some provider groups disagree regarding which screening tests are appropriate (Mahon, 2004). Although the debate has not altered CRC incidence rates since 1995, an approximately 1.7% decline in the mortality rate for men and women has occurred (ACS). When CRC is detected at an early, localized stage, the five-year relative survival rate is 90%. This rate drops to 67% after the cancer has spread to adjacent organs or lymph nodes and 10% when distant metastases develop (ACS). Because of the decreased survival rate for patients with metastatic CRC, researchers have concentrated on finding new, effective agents to fight the disease.

Treatment for CRC may include surgery, radiation, and chemotherapy. The primary treatment is surgery for removal of the tumor and acquisition of samples of adjacent tissue and lymph nodes. Pathologic classification with the tumor, node, metastasis (TNM) staging system is important as a tool to direct physicians in further management and as a prognostic indicator. The Dukes’ system was used in the past, but the American Joint Committee on Cancer (2002) has recommended the TNM system because it provides greater detail and precision in the identification of prognostic subgroups. Most cancers of the colon and rectum are grouped after pathologic examination. Patients are staged by tumor
size, regional lymph nodes, and distant metastases. Other surgical interventions for the treatment of metastatic disease that improve patient survival may include the resection of metastatic sites in the liver, lungs, and elsewhere or cryosurgery and radioablation of liver metastases (National Comprehensive Cancer Network, 2003).

Radiation therapy has a major role in the neoadjuvant treatment of rectal cancers because it shrinks tumors before surgery, allowing for less extensive surgical procedures. Adjuvant radiation is given following surgery when the risk of recurrence is high. Both modalities are administered with concomitant low-dose chemotherapy (e.g., 5-FU) to potentiate the radiation treatments. Chemotherapy is used for treatment after initial surgery in an adjuvant setting when no remaining cancer is apparent but the risk of microscopic spread is present. Clinicians disagree about whether any benefit in survival exists for patients with stage IIA or IIB disease who receive chemotherapy. The American Society of Clinical Oncology’s (ASCO’s) policy does not recommend the routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer. However, some patient populations with stage II disease may be considered for adjuvant therapy, including those with inadequately sampled nodes, T4 lesions, perforations, or poorly differentiated histology (Benson et al., 2004). Chemotherapy is the primary treatment for colon cancer in stages III and IV. No single agent has been shown to be more effective as a first-line therapy than the antimetabolite 5-FU, which has been available for more than 40 years (de Gramont et al., 2000). Combining 5-FU with a modulating agent such as LV has shown increased response rates but has had no major impact on survival (“Modulation of Fluorouracil by Leucovorin,” 1992). Before oxaliplatin was approved by the U.S. Food and Drug Administration for CRC, combination therapy with 5-FU, LV, and irinotecan (i.e., the Saltz regimen) was the first-line therapy for metastatic CRC and had an overall response rate of 39.4% and a survival rate of 14.8 months, both of which are significantly higher than with either irinotecan or 5-FU and LV alone (Saltz, Locker, Pirotta,Elfing, & Miller, 1999).

One of the newer drugs, oxaliplatin became available in Europe in 1996 and was established for use as a single agent and in combination and salvage therapy for metastatic CRC (de Gramont et al., 2000). A multicenter, randomized, three-arm, controlled study comparing the efficacy and safety of oxaliplatin in previously treated patients was conducted in North America (Rothenberg et al., 2003). Oxaliplatin in combination with 5-FU and LV, 5-FU and LV alone, and single-agent oxaliplatin were compared, and response rates showed an increase in median time to progression from 2.7 to 4.6 months in the oxaliplatin, 5-FU, and LV arm (p < 0.001) (Rothenberg et al.). The study led to the initial approval of oxaliplatin in the United States as a second-line chemotherapy treatment for patients with metastatic CRC whose cancer had recurred or progressed after receiving the Saltz regimen.

Two studies published by the National Cancer Institute and led by the North Central Cancer Treatment Group have established oxaliplatin further as a leading chemotherapeutic agent in the treatment of CRC: Goldberg et al.’s (2004) study of previously untreated patients with advanced CRC who were given a combination therapy of oxaliplatin, 5-FU, and LV, and Andre et al.’s (2004) study evaluating the efficacy of oxaliplatin, 5-FU, and LV in the postoperative adjuvant setting.

**Oxaliplatin**

**Pharmacology**

Oxaliplatin is an organoplatinum complex in which the platinum atom is attached to a 1,2 diaminocyclohexane carrier ligand. Its cytotoxic effect is exerted through the induction of apoptosis, the formation of DNA adducts that block DNA replication, and transcription resulting in the cell death of actively dividing cells (Wilson et al., 2002). After a two-hour infusion, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is distributed rapidly into tissues and binds to albumin and gamma globulins (Sanofi-Synthelabo Inc., 2004). Oxaliplatin has a nonenzymatic metabolism that suggests minimal drug-to-drug interaction. Platinum compounds are eliminated via renal excretion. Clearance of unbound oxaliplatin is decreased in patients with mild, moderate, and severe renal impairment. The National Cancer Institute has published data on the use of oxaliplatin in renal impairment (CrCl > 20 ml per minute) (Takimoto et al., 2003). The increased levels of plasma-protein-bound and -unbound oxaliplatin did not correlate to increased systemic toxicities.

**Side Effects**

The side-effect profile of oxaliplatin is well documented. The most significant dose-limiting toxicity is a cumulative sensory neurotoxicity with reversible paresthesias and cold-induced dysesthesias (Grotehy, 2003). Other common side effects include fatigue, neutropenia, nausea, vomiting, and diarrhea, the incidences of which are increased when oxaliplatin is given in combination with 5-FU and LV (Wilkes, 2002). The incidence rates of HSRs also increased by as much as 10% in previously treated patients who received a median of six cycles of oxaliplatin, 5-FU, and LV and 12% in untreated patients who received a median of 10 cycles (Sanofi-Synthelabo Inc., 2004). Patients receiving oxaliplatin are at an increased risk for HSRs. A retrospective study concluded that oxaliplatin may cause HSRs in an estimated 12% of patients, twice as many as with platinum analogs such as cisplatin and carboplatin (Meyer, Zuberbier, Worm, Oettle, & Riess, 2002).

**Hypersensitivity Reactions**

HSRs to oxaliplatin were reported in the literature as case studies before the drug was approved in the United States (Larzilliare et al., 1999; Santini et al., 2001; Schull, Kornek, & Scheithauer, 2001; Stahl, Koster, & Wilke, 2001; Tournigand, Maindrault-Goebel, & Louvet, 1998). In each case study, patients received oxaliplatin, 5-FU, and LV as a second- or third-line treatment (see Table 1).

**Etiology**

The etiology of HSRs to oxaliplatin is unclear; no single biologic pathway has been implicated, and HSRs may be caused by a combination of immunologic responses. HSRs occur when the immune system identifies a chemotherapeutic agent as an antigen substance, which results in antibody production, histamine release, and subsequent sensitization of T lymphocytes and macrophages (Zanotti & Markman, 2001). The most common reaction to chemotherapy (i.e., type 1) is immediate immunoglobulin E-mediated HSRs with mast cells and basophil degranulation (Zanotti & Markman). Release of cytokines such as tumor necrosis factor-alpha or interleukin-6 is elevated during an oxaliplatin HSR but returns to normal with symptom resolution (Tonini et al., 2002). In addition, Thomas, Quinn, Schuler, and Grem (2003) described a different type of HSR or idiosyncratic reaction that is not antibody related and the onset of which is delayed instead of immediate. The clinical features, therefore, are categorized as immediate (i.e., hyper-
sensitivity) or delayed by several hours (i.e., idiosyncratic) (Thomas et al.). Idiosyncratic reactions are less common with oxaliplatin but may include symptoms such as delayed fever or vomiting.

**Manifestations**

Manifestations are unpredictable and variable in incidence and severity. In their retrospective study, Brandi et al. (2003) found that risk factors or predictors of HSR severity could not be identified. Thirteen percent of patients developed HSRs after multiple infusions (i.e., 7–10 cycles), with symptoms developing quickly after the start of the infusion, suggesting a type I HSR (Brandi et al.). In fact, heavily pretreated patients may experience more severe adverse reactions (e.g., hypersensitivity, pain) (Lenz, Hacker, Kern, Schalhorn, & Hiddeman, 2003); however, the small, retrospective study examined patients with metastatic colon cancer receiving three different treatment regimens without premedication. In an abstract presented at ASCO, Dold et al. (2002) concluded that oxaliplatin HSRs usually occur during or shortly after administration in patients who have had multiple courses of treatment and are resolved without permanent sequela. Oxaliplatin HSRs affect a variety of body systems; the most frequently observed and reported symptoms are summarized in Table 2 and may include flushing, pruritis, confusion, tremors, hypotension, bronchospasm, and the sudden onset of nausea and vomiting. The most serious and life-threatening reaction is anaphylactic shock, which requires immediate emergency treatment. Although most HSRs are reported at the beginning of an oxaliplatin infusion, they may occur at any time during the infusion. The reactions may be mild, moderate, or severe and generally have a sudden onset.

**Treatment of Oxaliplatin Hypersensitivity Reactions**

Immediate recognition of an HSR and intervention are imperative to minimize symptom progression and systemic decompensation. Nurses should initiate symptom management and resuscitation measures, notify the physician, and closely monitor cardiovascular and respiratory status. The infusion of oxaliplatin and any other drugs should be stopped, and rapid rate normal saline should be started and titrated to maintain blood pressure. Airway management and oxygenation are priorities in severe cases, and supplemental oxygen should be given if a patient experiences decreased oxygen saturation, bronchospasm, laryngospasm, or dyspnea. Because the immunologic pathway that causes HSRs is unknown, several pharmacologic interventions are recommended for mild, moderate, and severe reactions. Corticosteroids with a rapid onset of action (i.e., Solucortef® [Pharmacia & Upjohn Co., Kalamazoo, MI] 100–1,000 mg) should be given via IV at the beginning of an HSR as determined by the physician and in response to the severity of the reaction (Brandi et al., 2003). Antihistamines such as the histamine-1 antagonist diphenhydramine (50 mg) should be given via IV (Bhargava, Gammon, & McCormick, 2003; Brandi et al.; Thomas et al., 2003). In cases of severe anaphylaxis or anaphylactoid reaction, 0.3–0.5 mg of epinephrine in a 1:1,000 solution should be administered subcutaneously and repeated at 20-minute intervals (Ahya, Flood, & Paranjothi, 2001). In most mild to moderate cases of HSR, symptoms resolve in 20–30 minutes; however, some reactions can persist for hours and necessitate hospital admission for supportive care and observation.

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integumentary</td>
<td>Flushing, pruritus or burning pruritis, diaphoresis, generalized erythema, hives, band or trunk erythema, edema, facial edema</td>
</tr>
<tr>
<td>Central nervous</td>
<td>Confusion, tremors, visual disturbances, dizziness, lacrimation</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, hypertension, tachycardia, palpitations, precordial pain</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Decreased oxygen saturation, bronchospasm, laryngospasm, wheezing, sneezing, dyspnea, respiratory distress</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea, abdominal cramping</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Fever, chills</td>
</tr>
<tr>
<td>Whole body</td>
<td>Angioedema, anaphylaxis</td>
</tr>
</tbody>
</table>

**Prophylaxis and Retreatment**

Retreatment with oxaliplatin following an HSR is not recommended by the manufacturer. However, when other treatment modalities have failed in patients with advanced CRC who have a favorable response to oxaliplatin, reexposure to the drug, along with a regimen of prophylactic medication, has been attempted. Brandi et al. (2003) used an immunologic blockage with high-dose steroids and antihistaminic drugs for several days before oxaliplatin infusion, but the benefit was unclear because five of six patients treated with steroids and/or antihistaminic drugs immediately before reexposure to oxaliplatin developed the same intensity of HSR. Dold et al. (2002) reported that no patient premedicated with dexamethasone (20 mg), cimetidine (300 mg), diphenhydramine

**Table 1. Hypersensitivity Reaction Case Report Summaries**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>N</th>
<th>CYCLES</th>
<th>SYMPTOMS</th>
<th>STEROID PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tournigand et al., 1998</td>
<td>5</td>
<td>5, 7, 8, and 12</td>
<td>Hypotension, flushing, diaphoresis, dizziness, tachycardia, burning sensation, pricking sensation in the mouth, headache, respiratory distress</td>
<td>No</td>
</tr>
<tr>
<td>Larzilliere et al., 1999</td>
<td>1</td>
<td>6</td>
<td>Flushing, diaphoresis, hypertension, tachycardia</td>
<td>Yes</td>
</tr>
<tr>
<td>Santini et al., 2001</td>
<td>1</td>
<td>3 and 6</td>
<td>Hypotension, nausea, vomiting, diarrhea, fever, chills</td>
<td>No</td>
</tr>
<tr>
<td>Schull et al., 2001</td>
<td>1</td>
<td>5</td>
<td>Hypotension, flushing, erythema trunk</td>
<td>No</td>
</tr>
<tr>
<td>Stahl et al., 2001</td>
<td>2</td>
<td>8 and 9</td>
<td>Cough, nausea, dyspnea, flushing, erythema trunk, sudden and repeated sneezing</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Bhargava et al., 2003; Brandi et al., 2003; Dold et al., 2002; Larzilliere et al., 1999; Lenz et al., 2003; Meyer et al., 2002; Santini et al., 2001; Schull et al., 2001; Stahl et al., 2001; Thomas et al., 2003; Tournigand et al., 1998.
(25 mg), acetaminophen (650 mg), grani-
estron (1 mg), and dextrose (500 ml, 5% in
saline) and given an oxaliplatin infusion
over six hours instead of the usual two
hours developed a reaction. Bhargava et al.
(2003) reported in a case study that despite
premedication with oral dexamethasone
beginning 24 hours before chemotherapy,
administration of IV dexamethasone and
diphenhydramine 30 minutes before treat-
ment, and reduction of the infusion rate
by 50%, the patient experienced a similar
HSR approximately 20 minutes after the
oxaliplatin infusion was initiated. In their
review of hypersensitivity and idiosynchratic
reactions to oxaliplatin, Thomas et al. (2003)
concluded that patients who develop mild
to moderate HSRs may be pretreated with
steroids and type 1 or 2 histamine receptor
antagonists, whereas patients who develop
severe reactions are unlikely to tolerate
further therapy.

Desensitization protocols have been used
with other platinum analog drugs such as
cisplatin and carboplatin and have been
suggested for use with oxaliplatin. Two case
studies described a desensitization protocol
in which oxaliplatin was administered suc-
cessfully in increasing dilutions and given
over a longer period of time (Bhargava et
al., 2003; Meyer et al., 2002). Using a de-
sensitization regimen may allow clinicians
to continue treatment with oxaliplatin in
patients who have experienced severe HSRs
and exhausted other treatment options for
CRC (Bhargava et al.). The data regarding
desensitization protocols with other plati-
num analogs are more extensive than with
oxaliplatin. For example, Bhargava et al.
adapted a carboplatin protocol that used seri-
al dilutions to desensitize patients. Dilutions
begin at 1:1,000 and decrease to 1:10 and
1:10, each in 50 ml of 5% dextrose in water.
Other protocols use extensive premedica-
tions (e.g., dexamethasone, H1 antagonists,
H2 antagonists) as well as serial dilutions
(Markman et al., 2003) (see Table 3).

**Implications for Nursing Practice**

HSRs occur in 10%--12% of patients
receiving oxaliplatin. HSRs occur most
frequently after patients receive multiple
cycles and are more prevalent in heavily
pretreated patients. Nurses should assess
patients accurately by carefully recording
their history of other drug sensitivities and
drug allergies. Although cross-sensitivity
with other platinum analog drugs is docu-
menced in the literature (Meyer et al.,
2002), most patients with CRC have not
been exposed to carboplatin or cisplatin
because these drugs are not indicated for
CRC.

Patients’ physical examinations should
include assessment of baseline vital signs
and the skin, cardiovascular system, and
respiratory system. Nurses must be vigilant
when observing patients during oxaliplatin
infusion. Most HSRs occur within minutes
of administration (Sanofi-Synthelabo Inc.,
2004) but can begin at any time during
the two-hour infusion. Prompt recognition
and administration of supportive care are
imperative to alleviating symptoms and
preventing life-threatening complications.
HSRs still may occur if patients have been
premedicated. Patients must be educated
about the side effects of oxaliplatin and the
possibility of an HSR during therapy and be
reassured that they will be observed closely
to assess for cardiac or respiratory compromise.

If an HSR or anaphylaxis is suspected,
nurses should stop all drug infusions imme-
diately, notify the physician, and assess the
patient for cardiac or respiratory compromise.
The ABC rules of resuscitation should be
followed: airway, breathing, and circulation.
An emergency plan should be in place, and
nurses must know the appropriate algorithm
for their hospitals or outpatient facilities.
Appropriate pharmacologic and oxygen therapy
should be given as directed by the plan or
the physician in charge. In most cases, HSRs
will subside in 20–30 minutes, but they have
progressed for as long as nine hours (Larzil-
liere et al., 1999; Meyer et al., 2002; Santini
et al., 2001; Stahl et al., 2001; Tonini et al.,
2002; Tournigand et al., 1998). In cases of
cardiovascular collapse and when patients are
unresponsive to bolus normal saline infusion
or experience severe respiratory compromise
or airway obstruction, they should be admit-
ted immediately to the intensive care unit for
emergency treatment.

HSRs are very frightening to patients
and produce elevated levels of anxiety or
excitability, feelings of impending doom,
confusion, and, in rare cases, altered levels
of consciousness if patients are severely
hypotensive. Constant communication
and reassurance help patients and families
remain calm.

Documentation and definition of the
HSR should be quantified according to the
National Cancer Institute’s (1999) grading
system for toxicity of allergic reactions and
HSRs (see Table 4). The documentation of
the HSR also should include detailed de-
scriptions of the adverse effects, their onset
and duration, the management protocol
implemented, and the patient’s response
to treatment.

If a patient develops a mild allergic reaction
manifested by hives or a rash, premedicating
with an antihistamine and a corticosteroid is
recommended in addition to increasing the
length of the infusion to six hours (Brandi et
al., 2003). However, rechallenging patients
with oxaliplatin on the same day that they
develop oxaliplatin reactions is not recom-
manded, and reexposure is contraindicated
if symptoms recur after patients are given
premedications before the next cycle (Sorich,
Taubes, Wagner, & Hochster, 2004).

**Conclusion**

Oxaliplatin is a novel chemotherapy med-
ication for CRC that presents challenges
in recognizing and treating HSRs and anaph-
ylactic reactions. In most cases, the drug
can be administered safely with close obser-
vation and careful monitoring. Nurses must
be familiar with oxaliplatin’s side effects,
pretreatment regimens, the possibility of
HSRs after repeated dosages, and manage-
ment strategies to control symptoms. Because
CRC is the third-leading cause of cancer
death in men and women, new therapies and
combination regimens are being used to treat
the disease and prolong life. Before the ap-
proval of oxaliplatin in 2002, only a few drugs
were indicated for the treatment of advanced
metastatic CRC. Oxaliplatin has given new

---

**Table 3. Desensitization Protocol for Platinum Chemotherapy Analogs**

<table>
<thead>
<tr>
<th>Step</th>
<th>Dilution</th>
<th>Example Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1,000</td>
<td>0.09 mg oxaliplatin in 50 ml 5% dextrose in water over 30 minutes</td>
</tr>
<tr>
<td>2</td>
<td>1:100</td>
<td>0.9 mg oxaliplatin in 50 ml 5% dextrose in water over 15 minutes</td>
</tr>
<tr>
<td>3</td>
<td>1:10</td>
<td>9 mg oxaliplatin in 50 ml 5% dextrose in water over 15 minutes</td>
</tr>
<tr>
<td>4</td>
<td>Remainder of dose</td>
<td>90 mg oxaliplatin in 250 ml 5% dextrose in water over 60 minutes</td>
</tr>
</tbody>
</table>

*Each dose is given in succession if the previous dose is tolerated.*

hope to patients with this devastating disease. Management and early recognition of HSRs may allow for prolonged courses of treatment with greater control of metastatic disease and improved disease-free survival when used in the adjuvant setting.

Author Contact: Kathleen Bonosky, RN, BSN, OCN®, can be reached at kbonosky@wpahs.org, with copy to editor at CJON editor@jsobel.com.

References


---

**TABLE 4. COMMON TOXICITY CRITERIA OF THE NATIONAL CANCER INSTITUTE**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ADVERSE EVENT</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Transient rash, drug fever &lt; 38°C (&lt; 100.4°F)</td>
<td>Urticaria, drug fever ≥ 38°C (≥ 100.4°F), asymptomatic bronchospasm</td>
<td>Symptomatic bronchospasm requiring parenteral medication, with or without urticaria; allergy-related edema, angioedema</td>
<td>Anaphylaxis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

**CLINICAL JOURNAL OF ONCOLOGY NURSING • VOLUME 9, NUMBER 3 • HYPERSENSITIVITY REACTIONS TO OXALIPLATIN**
Rapid Recap

Hypersensitivity Reactions to Oxaliplatin: What Nurses Need to Know

- Colorectal cancer is the third-leading cause of cancer-related death in the United States and historically has been treated with surgery, chemotherapy, and radiation.
- Oxaliplatin is approved for use in advanced colorectal disease and has been found to be more effective than past chemotherapy regimens when used in combination with 5-fluorouracil.
- Hypersensitivity reactions (HSRs) occur during administration of oxaliplatin in 10%–12% of patients.
- Manifestations of HSRs are variable in their incidence and severity and affect most body systems.
- Recognition, rapid intervention, and initiation of treatment protocols are imperative for minimizing symptoms and preventing systemic decompensation.
- Nurses must be vigilant in their observations and familiar with side effects and HSR symptoms, treatment, and pretreatment protocols to improve documentation and patient education.