

Oxaliplatin: A Novel Platinum Analog With Activity in Colorectal Cancer

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Purpose/Objectives: To review selected recent data pertaining to the use of oxaliplatin in colorectal cancer and its implications for oncology nursing.

Data Sources: Published articles, abstracts, and conference proceedings.

Data Synthesis: Colorectal cancer accounts for about 15% of all new cancers. The search for more effective chemotherapy regimens is ongoing. Oxaliplatin, a member of the diaminocyclohexane family of platinum compounds, demonstrates cytotoxic efficacy and a well-tolerated safety profile.

Conclusions: Oxaliplatin is effective in chemotherapy-naïve patients with advanced colorectal cancer, as well as in those refractory to previous treatment with 5-fluorouracil (5-FU); the drug also is effective in combination with 5-FU and leucovorin for the treatment of advanced colorectal cancer.

Implications for Nursing: Nurses must be highly knowledgeable about oxaliplatin regimens and schedules, the associated side effects, and recommended strategies for symptom management. This article can help nurses to understand and communicate the benefits and risks associated with oxaliplatin-based therapies to colleagues and patients.

According to estimates, more than 147,000 adults in the United States will be diagnosed with colorectal cancer in 2003, accounting for about 15% of all new cancers. This disease kills approximately 57,000 people each year, a rate second only to that of lung cancer, and the prognosis for patients with metastatic disease is especially poor, with only about 8% surviving five years (Jemal et al., 2003). Chemotherapy has demonstrated palliation of symptoms, increased survival, and improved quality of life compared with the best supportive care, but much room exists for improvement (Cunningham et al., 1998; Rougier et al., 1998). Four drugs have been approved by the U.S. Food and Drug Administration as single agents or as part of combination therapies for the treatment of metastatic colorectal cancer: 5-fluorouracil (5-FU), irinotecan (Camptosar®, Pharmacia Corporation, Peapack, NJ), capecitabine (Xeloda®, Roche Laboratories, Nutley, NJ), and oxaliplatin (Eloxatin®, Sanofi-Synthelabo, Inc., New York, NY).

Single-agent 5-FU is far from ideal, with response rates of less than 15% and overall survival rates of six to nine months (Becouarn & Rougier, 1998; Bleiberg, 1996; de Gramont et al., 2000; Schmoll, 1996). In the metastatic setting, the addition of leucovorin to the 5-FU regimen increased response rates to about 23%, but duration of survival, which only occasionally exceeds 12 months, did not increase significantly

Key Points . . .

- Oxaliplatin is a novel platinum compound with a wide spectrum of activity in oncology. One of its most notable qualities is its activity in colorectal cancer.
- In randomized clinical trials, oxaliplatin in combination with 5-fluorouracil and leucovorin has demonstrated significant improvements in response rates and progression-free survival but not overall survival.
- In-depth knowledge about oxaliplatin, its proper dosing and management, and the assessment and management of its adverse events will help to minimize the occurrence of problems and maximize treatment outcomes.

(Advanced Colorectal Cancer Meta-Analysis Project, 1992; Scheithauer, Rosen, Korneck, Sebesta, & Depisch, 1993). Therefore, agents that can achieve better results must be discovered.

Irinotecan, for example, has significant single-agent activity against colorectal cancer that has progressed during or shortly after treatment with 5-FU-based chemotherapy (Rothenberg et al., 1996). In addition, the combination of irinotecan, 5-FU, and leucovorin (IFL) has demonstrated a significant advantage in terms of response rate and, more importantly, overall survival rate compared with 5-FU plus leucovorin alone. Moreover, the IFL regimen is the standard treatment arm in many clinical trials that examine the efficacy of novel agents in metastatic colorectal cancer. Two independent trials reported responses with IFL that were double those seen with 5-FU and leucovorin. Saltz et al. (2000) reported a response rate of 39% versus 21% and an overall survival rate of 14.8 months versus 12.6 months in chemotherapy-naïve patients with metastatic disease who were treated with IFL versus 5-FU and leucovorin, respectively. Douillard et al. (2000) used irinotecan plus continuous-infusion 5-FU and leucovorin instead of the bolus schedule used in the Saltz et

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al. (2000) trial and reported a response rate of 41% compared with 23% and an overall survival rate of 17.4 months compared with 14.1 months for the IFL and 5-FU and leucovorin regimens, respectively.

Two large, independent, phase III clinical trials of capecitabine reported a significantly higher response rate with capecitabine compared with 5-FU and leucovorin injected via IV on a daily basis for five days once a month (i.e., the “Mayo” regimen) (Hoff et al., 2001; Van Cutsem et al., 2001). Despite the better response rate, the duration of response and survival were equivalent. The investigators concluded that capecitabine was at least equal to the Mayo regimen and that, as an oral agent, the drug was convenient and better tolerated (Hoff et al.; Roche Laboratories, 2001; Van Cutsem et al.). Capecitabine is indicated for patients with metastatic colorectal cancer when treatment with a fluoropyrimidine (e.g., 5-FU) monotherapy is preferred. However, capecitabine monotherapy did not demonstrate a survival benefit compared with 5-FU and leucovorin therapy, whereas the combination of IFL did show a survival benefit (Roche Laboratories). The use of capecitabine instead of 5-FU and leucovorin in IFL combination therapy is not recommended (Roche Laboratories).

Many clinical trials are investigating chemotherapy agents, especially for patients refractory to first-line therapies. This intense surge in the development of second-line treatments for advanced colorectal cancer refractory to 5-FU- and leucovorin-based therapy includes agents such as irinotecan, raltitrexed (Tomudex®, AstraZeneca, Wilmington, DE), cetuximab (Erbix™, ImClone Systems, New York, NY), and gefitinib (Iressa®, AstraZeneca), all of which have been or are being investigated (Findlay et al., 1997; Harper, 1997; Pazdur, 1998; Rothenberg et al., 1996; Sadahiro, Mukai, Tokunaga, Tajima, & Mitomi, 1998; Saltz et al., 2002; Von Hoff et al., 1997). These agents have shown varying clinical efficacy and safety profiles. With the exception of irinotecan, which has demonstrated a survival advantage when combined with 5-FU and leucovorin, none of the other agents is clearly superior for second-line treatment of advanced colorectal cancer. Oxaliplatin, a third-generation platinum compound, has been used extensively in Europe since the 1990s (Cvitkovic & Bekradda, 1999). Despite the lack of activity of the other platinum compounds (e.g., cisplatin, carboplatin) in colorectal cancer, oxaliplatin has demonstrated efficacy in the disease and is an effective addition to the colorectal cancer treatment armamentarium.

Background on Oxaliplatin

Oxaliplatin, a member of the diaminocyclohexane (DACH) family of platinum compounds, is a novel agent with demonstrated cytotoxic efficacy and a well-tolerated safety profile. Until recently, cisplatin and its analog carboplatin, the only platinum agents available to treat malignancies, were considered inactive against colorectal cancer. Oxaliplatin showed in vitro activity against colon cancer cell lines that are resistant to cisplatin and carboplatin (Rixe et al., 1996), which led to its development as an antineoplastic agent.

Mechanism of Action

Platinum compounds, including oxaliplatin, are alkylating agents that prevent DNA synthesis by directly damaging

DNA strands. DNA replication and transcription are prevented by cross-linking of the strands. Whereas cisplatin and carboplatin have a common *cis*-diamine complex, oxaliplatin differs molecularly by its bulky 1,2-DACH carrier ligand that investigators hypothesize accounts for both its efficacy and lack of cross-resistance with other platinum compounds. The complexes bind to DNA, producing inter- and intrastrand cross-links (Finley, 1991). This binding results in the formation of DNA platinum adducts that are believed to inhibit DNA replication and repair, although the exact mechanism by which the adducts cause cell death is uncertain (Colvin, 1997; Raymond, Faivre, Woynarowski, & Chaney, 1998; Reed, 1993).

Mechanisms of Platinum Resistance

Tumor cells can be inherently resistant to cisplatin or carboplatin or can develop acquired resistance. Studies have shown that oxaliplatin is active in some tumors that are not sensitive to cisplatin (Rixe et al., 1996; Silvestro, Anal, Sommer, Trincal, & Taplero, 1990); this is believed to result from differences in mismatch repair and replicative bypass (Raymond, Faivre, et al., 1998).

The mismatch repair mechanism is an enzyme complex that is responsible for repairing breaks in DNA (Raymond, Faivre, et al., 1998). When a platinum-initiated adduct is formed and a mismatch occurs in cisplatin-sensitive cells, the mismatch repair mechanism is hypothesized to cause continual but futile repairs to the DNA strand opposite the adduct; this leads to gaps and strand breaks that eventually cause apoptosis and cell death (Drummond, Anthoney, Brown, & Modrich, 1996; Raymond, Faivre, et al.). In cisplatin-resistant cells, the mismatch repair mechanism does not respond and cell death does not occur. The mismatch repair enzyme complex may be prevented from binding to oxaliplatin-initiated adducts because of interference from the bulky DACH ring (Raymond, Faivre, et al.). Hence, the presence of mismatch repair-related genes does not confer resistance to oxaliplatin; cells resistant to cisplatin as a result of this mechanism, which may lead to treatment failure, are sensitive to oxaliplatin (Raymond, Faivre, et al.).

The second mechanism of cisplatin resistance, replicative bypass, also is inhibited with oxaliplatin. Simply put, the DNA bypasses the damaged area and repairs the strand past the site of damage. The bulky DACH ring of oxaliplatin affects the ability of the replicating DNA to bypass the adduct, thereby resulting in apoptosis (Raymond, Faivre, et al., 1998; Vaisman, Varchenko, & Chaney, 1997).

Although clearly able to withstand resistance mechanisms that render cisplatin and carboplatin ineffective, oxaliplatin should not be expected to be effective in all cisplatin-resistant cell lines. Studies have shown that cell clones can develop with moderate resistance to cisplatin and carboplatin and high resistance to the DACH platinum compounds (Hills et al., 1989; Perez, O'Dwyer, Handel, Ozols, & Hamilton, 1991).

Clinical Trials With Oxaliplatin

Single Agent

Five phase II clinical trials have evaluated the efficacy and safety of single-agent oxaliplatin in patients who were chemotherapy naive (two trials, 63 patients) or who were refractory to previously administered chemotherapy (three trials, 139

patients) (Becouarn & Rougier, 1998; Diaz-Rubio et al., 1998; Levi et al., 1993; Machover et al., 1996). These trials demonstrated response rates of 10%–24%, median durations of response of 5–7 months, and median overall survival of 8–14.5 months.

Despite these relatively good results, single-agent use of oxaliplatin is not recommended in most patients with advanced colorectal cancer because treatment with IFL, single-agent 5-FU, or oxaliplatin in combination with 5-FU is considered more efficacious (Becouarn & Rougier, 1998). The exceptions are patients with a dihydropyrimidine dehydrogenase deficiency, which is associated with increased risk of severe or lethal 5-FU toxicity, or patients with cardiotoxicity from 5-FU (Milano & Etienne, 1996). In these cases, treatment with single-agent oxaliplatin may be appropriate.

Combination Regimens

Numerous phase II studies of oxaliplatin in combination with 5-FU and leucovorin for the treatment of advanced colorectal cancer in patients previously treated with 5-FU have been conducted. These trials have used a variety of regimens with different dosage and administration schedules (e.g., continuous infusion, chronomodulated [circadian rhythm], IV bolus). Response rates of 21%–48%, median progression-free survival of 5–9 months, and median overall survival of 11–18 months have been reported in patients with metastatic disease who were treated previously (Schmoll & Cassidy, 2001). In addition, these trials have demonstrated two important effects: (a) the synergistic effect between oxaliplatin and 5-FU and (b) oxaliplatin added to 5-FU can, at least partially, overcome clinical resistance to previous 5-FU therapy (Schmoll & Cassidy).

In previously untreated patients with advanced colorectal cancer, phase II clinical trials of 5-FU plus oxaliplatin have reported response rates of 29%–55%, with median progression-free survival of 8–11 months and median overall survival of almost 15 months (Levi et al., 1992, 1994; Levi, Zidani, & Misset, 1997). Moreover, results show that the high rate of major tumor shrinkage from oxaliplatin plus 5-FU has converted 16% of patients with initially unresectable liver metastases into surgical candidates. In these patients, 54% and 30% were alive at three and five years, respectively, after partial hepatectomy (Bismuth & Adam, 1998). These studies led to phase III clinical trials with the 5-FU and leucovorin combination.

Two phase III clinical trials conducted in Europe designed to evaluate the addition of oxaliplatin to 5-FU-based chemotherapy regimens for advanced colorectal cancer demonstrated efficacy (de Gramont et al., 2000; Giacchetti et al., 2000). Both studies were multicenter, open-label, randomized trials. Patients were chemotherapy naive or had not received adjuvant chemotherapy for at least six months before entering the study. In the Giacchetti et al. trial, patients were randomized to either a 5-FU and leucovorin regimen administered as a chronomodulated infusion of 5-FU 700 mg/m² and leucovorin 300 mg/m² for five days or they received the same regimen with the addition of oxaliplatin 125 mg/m² administered over six hours. The infusions were delivered using a multi-channel, programmable pump in an outpatient setting, and regimens were repeated every three weeks. In the de Gramont et al. trial, patients were randomly assigned to receive 5-FU and leucovorin or 5-FU, leucovorin, and oxaliplatin. The 5-

FU and leucovorin were administered as leucovorin 200 mg/m² and a bolus 5-FU dose of 400 mg/m², followed by a 22-hour continuous infusion of 5-FU 600 mg/m² for two consecutive days. Patients assigned to receive 5-FU, leucovorin, and oxaliplatin were administered the same dosage regimen of 5-FU and leucovorin as noted above with the addition of 85 mg/m² of oxaliplatin as a two-hour infusion on day 1. Treatments were conducted in an outpatient setting, and regimens were repeated every two weeks.

Results for the Giacchetti et al. (2000) and de Gramont et al. (2000) trials are shown in Table 1. The overall response rates and median progression-free survival were significantly greater for patients who received oxaliplatin than for patients who did not; however, the median overall survival rate was similar in both treatment groups in both trials. The similarity in overall survival may be related to the small sample size and crossover effect. In the Giacchetti et al. and de Gramont et al. trials, 57% and 37%, respectively, of patients who initially received only 5-FU and leucovorin also received second-line oxaliplatin-based therapy. When only patients who had not received second-line therapy with these agents were considered, median survival was 12.2 months for those who received 5-FU and leucovorin alone versus 14.8 months for those who received oxaliplatin ($p = 0.04$) (de Gramont et al.).

Although adverse events were more frequent with the oxaliplatin combination than with 5-FU and leucovorin alone, they were managed easily. The notable adverse events ($p = 0.001$) in the Giacchetti et al. (2000) trial were nausea and vomiting (2% with 5-FU and leucovorin; 25% with 5-FU, leucovorin, and oxaliplatin) and diarrhea (5% with 5-FU and leucovorin; 43% with 5-FU, leucovorin, and oxaliplatin). Sensory neuropathy occurred in 13 patients receiving the oxaliplatin-containing treatment, resulting in moderate functional impairment. Both treatments were well tolerated in the de Gramont et al. (2000) trial. Grade 3 or 4 adverse events that were significantly different between treatments were neutropenia (5% versus 42%, $p < 0.001$), nausea and vomiting (2% versus 6%, $p = 0.043$), diarrhea (5% versus 12%, $p = 0.015$), and mucositis (2% versus 6%, $p = 0.019$) for 5-FU and leucovorin versus oxaliplatin, 5-FU, and leucovorin, respectively (de Gramont et al.). Peripheral sensory symptoms in oxaliplatin-treated patients included acute cold-related manifestations in 68% of patients and transient pharyngolaryngeal spasm in 1% of patients. Functional impairment from cumulative paresthesia occurred in 16% of patients after a median total dose of 874 mg/m² and 10 cycles of treatment. Improvements in symptoms were noted in 74% of patients after a median time of 13 weeks (de Gramont et al.).

A third randomized phase III trial involving 252 patients with advanced colorectal cancer recently was reported by Grothey et al. (2002). The study compared the Mayo regimen with oxaliplatin administered over two hours plus 5-FU administered over 24 hours and folinic acid, which is another name for leucovorin, administered on days 1, 8, 15, and 22 every five weeks. Grothey et al. reported significant improvement in response rates and progression-free survival for patients who received oxaliplatin than for patients who did not. Overall survival was four months longer in patients treated with oxaliplatin than in those treated only with the Mayo regimen, although the difference was not statistically significant. Neutropenia was less severe with the oxaliplatin-containing treatment

Table 1. Randomized Trials of 5-Fluorouracil and Leucovorin and 5-Fluorouracil, Leucovorin, and Oxaliplatin in Patients With Advanced Colorectal Cancer

| Study | Treatment Arm | Patients (n) | Response Rate (%) | p | Median PFS (months) | p | Median OS (months) | p | Follow-Up Surgery for Metastases (%) |
|--------------------------|------------------------------|--------------|-------------------|----------|---------------------|----------|--------------------|----|--------------------------------------|
| Giacchetti et al. (2000) | 5-FU and LV CM | 100 | 16 | < 0.0001 | 6.1 | 0.0480 | 19.9 | NS | 21 |
| | Oxaliplatin + 5-FU and LV CM | 100 | 53 | | 8.7 | | 19.4 | | 32 |
| de Gramont et al. (2000) | 5-FU and LV | 210 | 22 | 0.0001 | 6.2 | 0.0001 | 14.7 | NS | 3 |
| | Oxaliplatin + 5-FU and LV | 210 | 50 | | 9.0 | | 16.2 | | 7 |
| Grothey et al. (2002) | 5-FU and LV | 124 | 23 | < 0.0001 | 5.3 | < 0.0001 | 16.1 | NS | NA |
| | Oxaliplatin + 5-FU and LV | 118 | 48 | | 7.9 | | 20.4 | | NA |

CM—chronomodulated; 5-FU—5-fluorouracil; LV—leucovorin; NA—not applicable; NS—not significant; OS—overall survival; PFS—progression-free survival

than with the Mayo regimen (7% and 23%, respectively); nonhematologic toxicities were comparable (Grothey et al.). The encouraging results of the European trials, coupled with the positive European clinical practice experience, led to the development of the U.S. clinical trial program.

U.S. Clinical Trials With Oxaliplatin Alone or in Combination

In the United States, a multivariate, open-label, compassionate-use trial allocated patients to one of six regimens chosen by investigators, as outlined in Table 2 (Mitchell, 2000); 1,131 patients were enrolled in this trial. Patients had been treated with an average of two prior cycles of chemotherapy before study entry. Time to discontinuation because of treatment failure was 3.5 months overall (2.8 months for the single-agent arm, 3.6 months for the combination cohorts) (Mitchell). The toxicity profile in this compassionate-use trial was consistent with that reported in patients treated in the de Gramont et al. (2000) and Giacchetti et al. (2000) phase III trials (Mitchell). Oxaliplatin either alone or with commonly used 5-FU regimens was well tolerated and offered a treatment option in patients who failed prior chemotherapy.

A large phase III clinical trial (protocol EFC 4584) has been conducted with oxaliplatin alone or in combination in patients who had failed prior irinotecan-based chemotherapy. In this

trial, patients were randomized to 5-FU and leucovorin, single-agent oxaliplatin, or 5-FU, leucovorin, and oxaliplatin as second-line treatment of metastatic colorectal cancer. This study included approximately 800 patients and evaluated efficacy, survival, tumor-related symptoms, and safety (National Cancer Institute, 2002b). In analysis planned to take place after 450 patients were enrolled, patients treated with oxaliplatin and an infused 5-FU and leucovorin combination had an increased response rate compared with the other two arms (9% oxaliplatin, 5-FU, and leucovorin versus 1% oxaliplatin alone versus 0% 5-FU and leucovorin) (Sanofi-Synthelabo, Inc., 2002). The median time to tumor progression also was better for those treated with the oxaliplatin combination (4.6 months of oxaliplatin, 5-FU, and leucovorin versus 1.6 months of oxaliplatin alone versus 2.7 months of 5-FU and leucovorin). Median overall survival was not statistically different between the 5-FU and leucovorin arm and the combination arm of 5-FU, leucovorin, and oxaliplatin (8.7 months versus 9.8 months, respectively) or between the 5-FU and leucovorin arm and single-agent oxaliplatin (8.7 months versus 8.1 months, respectively) (Rothenberg et al., 2003). The side effects reported in this trial are comparable to those seen in other oxaliplatin-based trials in patients with colorectal cancer. Persistent peripheral neuropathy occurred in 48% of patients in the combination arm and in 43% of patients in the oxaliplatin-alone arm (Sanofi-Synthelabo, Inc., 2002). Other common toxicities included diarrhea, nausea, vomiting, leukopenia, and neutropenia. Results of this pivotal trial were submitted to and used by the U.S. Food and Drug Administration to clear oxaliplatin for marketing in the United States.

Ongoing U.S. Clinical Trials

Preliminary results from a planned interim analysis on protocol N9741, a phase III clinical trial being conducted by the U.S. Intergroup, were reported at a meeting of the American Society of Clinical Oncology (Goldberg et al., 2002). Although the trial protocol has been modified many times, patients ultimately were randomized to IFL, oxaliplatin plus infused 5-FU (FOLFOX 4), or irinotecan plus oxaliplatin. A preliminary analysis revealed that patients receiving FOLFOX 4 fared significantly better than those receiving IFL. The response rate was 38% versus 29%, time to tumor progression was 8.8 months versus 6.9 months, and the overall survival

Table 2. U.S. Compassionate-Use Trial of Oxaliplatin With 5-Fluorouracil or as a Single Agent in Metastatic Colorectal Cancer

| Regimen | Patients Treated (%) |
|---|----------------------|
| Single-agent oxaliplatin | 11 |
| Oxaliplatin plus 5-fluorouracil and leucovorin | 89 |
| Daily for five days | 15 |
| Weekly for six weeks of eight | 41 |
| Weekly high-dose 5-fluorouracil | 5 |
| Bolus 5-fluorouracil and leucovorin with 22-hour infusion | 8 |
| Continuous infusion | 20 |

N = 1,131

Note. Based on information from Mitchell, 2000.

rate was 18.6 months versus 14.1 months for the FOLFOX 4 and IFL arms, respectively. At one year, 71% of patients treated with FOLFOX 4 were alive compared with 58% on the IFL arm. Incidence of severe toxicity also favored the oxaliplatin-based regimen with the exception of a notable sensory neurotoxicity. The survival advantage for patients treated with FOLFOX 4 may be enhanced further because of the second-line therapies administered to patients after discontinuation of study therapy. Fifty-two percent of patients received irinotecan as a second-line therapy because it is commercially available in the United States. Oxaliplatin was not commercially available at the time of study initiation; therefore, it was only available to a small percentage (17%) of patients who relapsed after IFL treatment. According to the National Cancer Institute (2002a), these differences in second-line therapy may account for some part of the observed difference in survival.

Another ongoing phase III trial (protocol EFC 4585) was designed to determine the overall survival of patients suffering from metastatic colorectal cancer that has progressed after first-line treatment with a regimen of 5-FU and leucovorin. These patients are randomized to receive irinotecan or oxaliplatin plus irinotecan. The study will evaluate response rate, time to tumor-related symptomatic worsening, time to disease progression, onset and duration of responses, duration of disease stabilization, and safety profile. Approximately 600 patients are expected to participate in the study (National Cancer Institute, 2002b).

Synergistic or additive cytotoxic effects have been reported with a variety of chemotherapy agents, including irinotecan, capecitabine, cisplatin, cyclophosphamide, gemcitabine, topotecan, raltitrexed, and paclitaxel (Raymond, Chaney, Taamma, & Cvitkovic, 1998). In metastatic colorectal cancer, oxaliplatin is being investigated in combination with irinotecan or capecitabine and in combination with IFL. Moreover, clinical trials are ongoing for many tumor types beyond metastatic colorectal cancer, such as ovarian, non-small cell lung, breast, pancreatic, and gastric cancers and non-Hodgkin's lymphoma.

Nursing Considerations With Oxaliplatin

Although experience with oxaliplatin is growing, many nurses are not yet familiar with its administration or toxicities. Oxaliplatin has a unique toxicity profile; however, adverse events can be avoided or ameliorated with proper handling and dosing of the drug as well as monitoring the onset of and management of adverse events.

Dose and Preparation

Oxaliplatin, used in combination with infused 5-FU and leucovorin, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within six months of first-line therapy with a combination of bolus 5-FU and leucovorin and irinotecan. The recommended dosage schedule for oxaliplatin is 85 mg/m² every two weeks. Oxaliplatin, available as a freeze-dried powder in 50 mg or 100 mg vials, is reconstituted with 10 ml or 20 ml, respectively, of sterile water for injection and then administered via IV in 250–500 ml of 5% dextrose in water (D₅W) (Sanofi-Synthelabo, Inc., 2002). All IV tubing must be flushed with D₅W before and after infusion of oxaliplatin. Oxaliplatin is unstable in normal

saline, cannot be combined with 5-FU or other alkaline solutions, and cannot be administered through needles or infusion sets containing aluminum components because of the potential for degradation (Sanofi-Synthelabo, Inc., 2002). In addition, unlike other platinum analogs, pre- or post-IV hydration or mannitol diuresis is not required (Extra, Marty, Brienza, & Misset, 1998; Pazdur, 1998).

Administration

The recommended dosage schedule, given every two weeks, is as follows.

Day 1: Oxaliplatin 85 mg/m² via IV infusion in 250–500 ml D₅W and leucovorin 200 mg/m² infusion in D₅W are administered simultaneously over 120 minutes in separate bags using a Y-line, followed by 5-FU 400 mg/m² via IV bolus given over two to four minutes. Next, 5-FU 600 mg/m² via IV infusion in 500 ml D₅W (recommended) is given as a 22-hour continuous infusion (Sanofi-Synthelabo, Inc., 2002).

Day 2: Leucovorin 200 mg/m² as an IV infusion is given over 120 minutes, followed by 5-FU 400 mg/m² via IV bolus administered over two to four minutes. Then, 5-FU 600 mg/m² via IV infusion in 500 ml D₅W (recommended) is given as a 22-hour continuous infusion.

Toxicity Profile

As demonstrated in clinical trials, the safety profile of oxaliplatin is differentiated clearly from other platinum compounds, and oxaliplatin-associated toxicities generally are manageable. Unlike cisplatin, oxaliplatin does not cause nephrotoxicity or motor neuropathy (Extra et al., 1998; Levi, Metzger, Massari, & Milano, 2000). Oxaliplatin produces less hematologic toxicity than carboplatin. Gastrointestinal toxicities, quite common with platinum compounds, are less common with oxaliplatin (Becouarn & Rougier, 1998). The dose-limiting toxicity is neurotoxicity (Sanofi-Synthelabo, Inc., 2002).

The toxicity profile of an oxaliplatin-based regimen varies depending on whether it is given alone or in combination with 5-FU and leucovorin. Moreover, variability exists according to the specific dose and schedule of 5-FU and leucovorin. For example, the weekly 5-FU and leucovorin regimen is associated with a higher incidence of diarrhea, whereas continuous-infusion schedules are associated with skin reactions. Oxaliplatin is noted for peripheral sensory neurotoxicity, which affects the total dose that patients can receive and can impair patients' ability to perform activities of daily living, thereby decreasing quality of life. Other common oxaliplatin-induced toxicities include gastrointestinal effects (e.g., nausea, vomiting, diarrhea) and hematologic toxicities (e.g., neutropenia, thrombocytopenia) (Extra et al., 1998; Sanofi-Synthelabo, Inc., 2002). Less common toxicities include mucositis, pulmonary fibrosis, and allergic reactions, specifically hypotension, sweating, and erythrodermia (Extra et al., 1998; Iirillo et al., 2000; Sanofi-Synthelabo, Inc., 2002).

Peripheral sensory neuropathy: Two types of peripheral nerves exist: sensory and motor. Sensory nerves are responsible for sensations such as pain, touch, temperature, position, and vibration; motor nerves are responsible for movement and the maintenance of muscle tone (Almadrones & Arcot, 1999). The dose-limiting and most severe oxaliplatin toxicity is primarily a peripheral sensory neuropathy that is exacerbated by cold temperatures. The exact mechanism for this phenomena

is unknown, but two theories exist. The acute sensory neuropathy is believed to be caused by an acquired inhibitory effect of the chelation of calcium ions by the oxaliplatin metabolite oxalate on the neuron voltage-gated sodium channel (Grolleau et al., 2001). The cumulative neurotoxicity has been associated with the formation of collagen pockets that result in a decrease in the density of small myelinated fibers causing changes in sensation (Extra et al., 1998). The most important risk factor for developing sensory neuropathy is the total cumulative dose of oxaliplatin. Extra et al. (1998) reported that, at cumulative doses of 780 mg/m², 10% of patients were at risk for developing severe neurosensory symptoms; at 1,170 mg/m², the risk rose to 50%, and at 1,560 mg/m², the risk increased to 75%. All patients experienced some sensory neuropathy after receiving four or more cycles of therapy with doses greater than or equal to 540 mg/m² (Extra et al., 1998). Ten percent of patients experienced severe symptoms after 6 cycles, 50% after 9 cycles, and 75% after 12 cycles when oxaliplatin was given at a dose of 130 mg/m² every three weeks (Wiseman, Adkins, Plosker, & Goa, 1999).

Transient paresthesias, commonly described as numbness and tingling in the fingers, hands, toes, or lips, and dysesthesias in the forearms, legs, mouth, and throat, initially characterize the neurosensory phenomena (Extra et al., 1990). These symptoms are enhanced by contact with cold and often regress between cycles of oxaliplatin, yet they tend to be more intense and last longer with subsequent cycles (Raymond, Chaney, et al., 1998). Functional impairment caused by sensory rather than motor changes, increasing difficulty with fine manual coordination, and moderate sensitive ataxia may occur as the total dose increases (Brienza, Vignoud, Itzhaki, & Krikorian, 1995). In a review of 34 patients, Gilles-Amar et al. (1999) reported that the median time to first occurrence of severe neuropathy was 15 weeks (eight two-week cycles), the median time to severe symptoms was 23 weeks, and the last occurrence was seen at 52 weeks. In general, the symptoms slowly reverse when the drug is discontinued before severe impairment occurs. The time to the first recovery from symptoms was two weeks, with a median time of 12 weeks (Gilles-Amar et al.). The likelihood of symptom regression is reported to correlate inversely with the total cumulative dose (Extra et al., 1998). Grade 1 or 2 neuropathy regressed in 82% of patients within four to six months and completely resolved in 41% of patients within six to eight months (Extra et al., 1998). In summary, the sensory neuropathy associated with oxaliplatin is specific, cumulative, and, unlike cisplatin-induced neuropathy, reversible in the majority of patients (Extra et al., 1998).

Acute laryngopharyngeal dysesthesias: This neurotoxicity is triggered or exacerbated by cold or can occur spontaneously during oxaliplatin infusion. Acute laryngopharyngeal dysesthesia is characterized by a spasm, a sensation of tightness in the throat, difficulty swallowing or speaking, or a feeling of not being able to breathe, without any objective sign of respiratory distress. This toxicity is very unsettling to patients and can occur when cold food or a cold beverage is consumed during the infusion or within several hours to days following oxaliplatin infusion (Raymond, Chaney, et al., 1998). If symptoms occur spontaneously during an infusion, oxaliplatin should be stopped temporarily. Patients should be observed until the symptoms abate and, if needed, treated symptomatically. Symptoms often reverse spontaneously without specific

medications, and after complete resolution, the infusion may be restarted at a slower rate (Sanofi-Synthelabo, Inc., 2002). Laryngopharyngeal dysesthesias usually are preventable with patient education regarding the effects of cold (Bleiberg, 1996; Pazdur, 1998; Pazdur & Vincent, 1997; Raymond, Chaney, et al.). Acute laryngopharyngeal dysesthesia has not been associated with discontinuation of therapy and can be prevented effectively by prolonging the infusion to six hours (Jansman, Sleijfer, de Graaf, Coenen, & Brouwers, 2001; Raymond, Chaney et al.).

Nurses' Role in Oxaliplatin-Induced Neuropathy

Patient assessment and education related to oxaliplatin-induced neurotoxicity are important responsibilities of oncology nurses. Unlike toxicities that are easily quantifiable (e.g., neutropenia) by a complete blood count and differential, the diagnosis of sensory peripheral neuropathy is difficult and often delayed (Almadrones & Arcot, 1999). Patients notice subjective changes early, which often remain unreported until an objective change occurs in gait or functional ability. Patient education must emphasize recognition of early signs and symptoms and ways to report changes, as well as information to assist patients in preventing exacerbations. Nurses must counsel patients to avoid exposure to cold for the first few days after treatment with oxaliplatin-based regimens (Berg, 2001, 2003; Wilkes, 2002). Avoiding exposure to air conditioning, freezers, refrigerators, and cold beverages and foods, especially within the first 48–96 hours of receiving oxaliplatin, is very important. For peripheral symptoms, patients should wear gloves and socks in cold weather or air conditioning. Gloves also should be worn to retrieve items from a refrigerator or freezer. Warm water, not cool or cold, should be used to wash the face, hands, and feet. In cold weather, cars should be warmed before patients get into them; in hot weather, air conditioning should be used carefully both in homes and in cars. For laryngeal symptoms, patients should drink beverages or eat foods that are warm or at room temperature (Berg, 2001, 2003; Wilkes); straws may be helpful in drinking liquids so that fluids can warm as they travel. In addition, insulated beverage holders may protect fingers and hands from cool drinks. Ice chips should not be used to prevent 5-FU-induced mucositis because this may exacerbate laryngopharyngeal dysesthesias. Acute neurotoxicities such as laryngopharyngeal dysesthesia may be related to the rate of oxaliplatin infusion; therefore, prolonging the infusion to four to six hours instead of the standard two hours should be considered (Cvitkovic & Bekradda, 1999; Sanofi-Synthelabo, Inc., 2002). Dosage reductions are important strategies in managing this toxicity (Raymond, Chaney, et al., 1998; Sanofi-Synthelabo, Inc., 2002).

Identifying patients at risk for developing neurosensory symptoms and carefully assessing their severity are important nursing functions. As previously noted, all patients develop some neurosensory symptoms at cumulative doses greater than or equal to 540 mg/m²; therefore, close monitoring should occur before this point in the treatment (Extra et al., 1998). Simple assessments of touch, position sense, vibration, and fine motor skills (e.g., buttoning clothing, picking up small items, writing, closing zippers, walking across a room) should be performed before each dose of oxaliplatin. Because intensity and duration factors must be assessed for cold-induced sensory neuropathies, the National Cancer In-

stitute Common Toxicity Criteria and the World Health Organization criteria are not helpful toxicity-grading tools. Therefore, European clinical investigators developed a neurotoxicity-grading scale to assess the severity of this unique toxicity that includes intensity and duration parameters (see Table 3). This grading scale also is used in the oxaliplatin clinical trials being conducted in the United States (Berg, 2001).

Three reports have been published about research concerning neurotoxicity from oxaliplatin. Rudolph, Ridwelski, Kuhn, and Lippert (2000) treated 27 patients with a combination of oxaliplatin, 5-FU, and leucovorin with or without amifostine. Patients completed a questionnaire daily to document side effects, in addition to undergoing neurologic examinations and laboratory analyses. Patients treated with amifostine showed a significant reduction in peripheral sensory neuropathy, leukopenia, and thrombocytopenia (Rudolph et al.). Mariani et al. (2000) wondered if gabapentin (Neurontin®, Pfizer Inc., New York, NY), an agent effective in neuropathic pain, could be the answer for oxaliplatin-induced neuropathy. Seven of the 10 patients in this study were treated with a combination of oxaliplatin, 5-FU, and leucovorin. Gabapentin was added at the onset of neuropathic symptoms. The starting dose was 100 mg twice daily, with a 100 mg per day increase in dose if symptoms did not resolve within three days. No patient required an initial dose escalation because all symptoms resolved. Two patients did require a dose increase during therapy because of a return of symptoms, but both responded to the higher dose. In all treated patients, the neurologic symptoms did not return, even after as many as 14 courses of therapy. No patient had to stop the chemotherapy regimen for neurotoxicity. Two patients spontaneously stopped taking gabapentin and noted a recurrence of neurologic symptoms that regressed once the agent was restarted (Mariani et al.). Gamelin et al. (2002) administered a

calcium gluconate and magnesium chloride infusion before and after oxaliplatin infusion to 63 patients and compared the results with those from the 38 patients in the control group. They concluded that the calcium and magnesium infusions reduced the incidence and severity of the sensory neuropathy and slightly reduced the cumulative neuropathy. A randomized, phase III, double-blind, placebo-controlled study is under way (Gamelin et al.).

Nonhematologic toxicity: In addition to sensory neuropathy, the nonhematologic side effects reported with oxaliplatin are nausea, vomiting, diarrhea, infrequent allergic reactions, and, rarely, pulmonary fibrosis. Additional toxicities are reported to be more pronounced when oxaliplatin is combined with 5-FU and leucovorin (depending on the specific regimen) and include mucositis, hand-foot syndrome, alopecia, and minor increases in hepatic enzymes (Bleiberg, 1996; Cvitkovic & Bekradda, 1999; Pazdur, 1998).

In early clinical trials, 70%–83% of patients receiving oxaliplatin at doses larger than 90 mg/m² experienced severe nausea and vomiting; none was premedicated with antiemetics (Raymond, Chaney, et al., 1998). After an unsuccessful attempt to reduce the nausea and vomiting by prolonging the infusion time, systemic premedication with a 5-HT₃ antiemetic decreased the incidence of grade 3 or 4 nausea and vomiting to 11% (Extra et al., 1990; Raymond, Chaney, et al.). Nausea and vomiting are rapid in onset and can last for 24–48 hours (Pazdur, 1998); therefore, all patients should be premedicated with a standard antiemetic regimen for platinum-based therapies.

Diarrhea is common, often is mild (grade 1 or 2), and occurs in about 25% of the cycles with single-agent oxaliplatin, with increased frequency when combined with 5-FU and leucovorin regimens (Extra et al., 1998; Wiseman et al., 1999). Diarrhea is usually of short duration and treated with antidiarrheal medications according to standard practice. Patients also may note abdominal cramping with or without diarrhea and inflammation or infection of the bowel (Sanofi-Synthelabo, Inc., 2002).

Skin reactions: Erythema, skin eruptions, and alopecia are uncommon when oxaliplatin is administered alone, but their incidence is higher when given in combination with 5-FU. Because oxaliplatin was administered as a continuous infusion in European trials, an implanted venous access port was required; soreness and redness at the IV site and muscle cramps in the arm used for treatment were not noted. These side effects may occur with peripheral IV administration and may last for several days after oxaliplatin infusion (Leichman et al., 2000; Sanofi-Synthelabo, Inc., 2002). Moist heat applied to the area where the drug is infused may be helpful. To date, two reports have been published about tissue necrosis induced by an oxaliplatin extravasation following administration through a peripheral vein (Baur, Kienzer, Rath, & Dittrich, 2000; Kennedy, Donahue, Hoang, & Boland, 2003). The drug is classified as a nonvesicant, but, in light of this report, that classification may need to be revisited.

Allergic reactions: Hypersensitivity reactions are associated with platinum compounds. Although uncommon with oxaliplatin, severe reactions have occurred in 1%–8% of patients and can occur during subsequent cycles of therapy even when previous cycles were well tolerated (Dold et al., 2002; Sanofi-Synthelabo, Inc., 2002). Rigors, dyspnea, fever, bronchospasm, itching, confusion, and laryngeal dysesthesia

Table 3. Oxaliplatin-Specific Neurologic Toxicity Scale for Clinical Trials

| Toxicity | Grade | Symptoms |
|-------------------------------|-------|---|
| Peripheral sensory neuropathy | 0 | None |
| | 1 | Paresthesias and dysesthesias of short duration that do not interfere with function and completely resolve before the next cycle |
| | 2 | Worsening paresthesias and dysesthesias of increasing severity, continuing between cycles, but without impairment of activities of daily living |
| | 3 | Functional impairment and impairment of activities of daily living (e.g., difficulty with buttoning and rapid writing, mild ataxia) |
| Laryngeal dysesthesias | 4 | Persistent paresthesias and dysesthesias that are disabling or life threatening |
| | 0 | None |
| | 1 | Mild |
| | 2 | Moderate |
| | 3 | Severe |

Note. Based on information from Sanofi-Synthelabo, Inc., 1998.

occurring during or shortly after the infusion are characteristic symptoms. In one study, an average of six doses were administered (range = 2–20) before the first hypersensitivity reaction (Dold et al.). Supplemental oxygen and symptomatic treatment are recommended. Differentiation between an allergic reaction and acute laryngopharyngeal dysesthesia is important because they share several common symptoms. Subsequent rechallenge with oxaliplatin after a mild hypersensitivity reaction is advisable. Dold et al. reported that, in 10 of 19 patients, subsequent doses of oxaliplatin were given after mild hypersensitivity reactions. All 10 patients were pretreated with dexamethasone 20 mg, cimetidine 300 mg, acetaminophen 650 mg, diphenhydramine 25 mg, and a six-hour infusion time. No patient experienced a repeat reaction (Dold et al.).

Hematologic toxicities: Single-agent oxaliplatin generally produces only mild to moderate hematologic toxicity, usually in the form of neutropenia or thrombocytopenia. Myelosuppression often resolves between cycles, but some patients develop chronic thrombocytopenia, with platelet counts of 75,000–90,000 u/L. Febrile neutropenia is uncommon. When oxaliplatin is combined with 5-FU and leucovorin, myelosuppression is a primary toxicity; the resulting severity of this toxicity is greater than with 5-FU and leucovorin alone (Bleiberg, 1996; Cvitkovic & Bekradda, 1999; Pazdur, 1998; Raymond, Chaney, et al., 1998; Wiseman et al., 1999). Dose modifications, as appropriate based on the level of myelosuppression, are recommended. Platelet transfusions may be required in some patients. No significant changes in hemoglobin have been reported (Extra et al., 1998). Hemolytic anemia is associated with cisplatin and carboplatin, and only one case of oxaliplatin-induced hemolytic anemia has been reported (Desrame, Broustet, Darodes de Tailly, Girard, & Saissy, 1999).

Conclusion

Oxaliplatin is a novel platinum compound with a wide spectrum of activity in cancer. This drug is distinct from cisplatin and carboplatin in pharmacology, cytotoxicity, mechanisms of resistance, and toxicity. One of its most notable differences is its activity in colorectal cancer. To date, in randomized clinical trials and actual clinical experience, oxaliplatin in combination with 5-FU and leucovorin has demonstrated significant improvements in response rates and progression-free survival but not overall survival. Beyond metastatic colorectal cancer, a number of clinical trials are investigating the activity of oxaliplatin plus 5-FU and leucovorin in adjuvant and neoadjuvant settings. Oxaliplatin has great potential to become part of the therapeutic regimen not only in colorectal cancer but also in many other solid tumors.


Patient assessment and education related to oxaliplatin-induced neurotoxicity are important responsibilities of oncology nurses. Because of the ongoing investigations with many other chemotherapy agents and in a variety of tumors, additional toxicities may be reported. Nurses must be highly knowledgeable about this agent and its various regimens and schedules, toxicity profile, and recommended symptom management strategies. Comprehensive information about oxaliplatin can help nurses to understand and communicate the benefits and risks associated with oxaliplatin-based therapies to colleagues and patients. The guidelines presented in this article may help to reinforce the need to balance the benefits and risks associated with oxaliplatin and help to optimize colorectal cancer therapy with oxaliplatin.

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For more information . . .

- CancerBacup: Understanding Oxaliplatin
www.cancerbacup.org.uk/info/oxaliplatin.htm
- Eloxatin
www.eloxatin.com
- MEDLINEplus Drug Information: Oxaliplatin
www.nlm.nih.gov/medlineplus/druginfo/uspdi/500411.html

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