Oxaliplatin-Related Side Effects: Characteristics and Management

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Oxaliplatin is the only third-generation platinum derivative to have found a place in routine cancer therapy. It is particularly useful therapy for advanced colorectal cancer and has shown scheduling flexibility in combination with 5-fluorouracil/folinic acid. Oxaliplatin has a unique pattern of side effects unrelated to those observed with other therapeutic platinum derivatives. During the course of oxaliplatin clinical trials, the adverse events most often cited were hematologic toxicity, gastrointestinal tract toxicity, and a neurotoxicity unlike that observed with other platinum derivatives. Grade 3/4 neutropenia occurred in 41.7% of patients in the phase III clinical trial that used the FOLFOX-4 regimen, and thrombocytopenia is a rare event sometimes observed after multiple cycles of therapy. Nausea and vomiting is usually mild to moderate and readily controlled with standard antiemetics. Grade 1/2 diarrhea may occur but studies have shown that 5-fluorouracil contributes significantly more to gastrointestinal toxicity than does single-agent oxaliplatin. Neutropoxygen has not been reported in any of the oxaliplatin trials, allowing administration of oxaliplatin without hydration. Oxaliplatin-induced neurotoxicity consists of a rapid-onset acute sensory neuropathy and a late-onset cumulative sensory neuropathy that occurs after several cycles of therapy. In about three fourths of patients, neurotoxicity is reversible with a median time to recovery of 13 weeks after treatment discontinuation. To date, oxaliplatin has proven to be a safe and effective therapy for colorectal cancer and side effects have been easy to manage with appropriate awareness from patients and care providers.

The THIRD generation of platinum derivatives, the 1,2-diaminocyclohexane (DACH) platinates, differ from previously developed agents such as cisplatin and carboplatin in that they do not present free amino groups linked to platinum, but rather a cyclic, bulky, rigid structure (Fig 1). DACH-platinates combine with DNA to form adducts resistant to DNA repair and replicative bypass.1 Of the several DACH platinum derivatives that have entered clinical development, oxaliplatin (trans-1,2-diaminocyclohexane-oxalatoplatinum (II)) is the only such agent to have successfully reached clinical use.

Preclinical studies in colon cancer cell lines have shown that the combination of oxaliplatin with both classical (5-fluorouracil [5-FU]) and nonclassical thymidylate synthase inhibitors exhibit significant cytotoxic synergy,2 as do combinations with topoisomerase I inhibitors3 and gemcitabine.4 In combination with traditional 5-FU/folinic acid (FA; leucovorin) regimens, oxaliplatin has shown significant activity against colorectal cancer,5-10 although modest activity as a single agent has also been seen.11 The combination of oxaliplatin with irinotecan has also shown significant clinical activity in early clinical trials.12-14

The various trials that have evaluated oxaliplatin in the treatment of colorectal cancer have shown the scheduling flexibility of the combination with 5-FU/FA. The regimens listed in Table 1 have provided improved response rates over conventional therapy. Biweekly and triweekly regimens at equal dose intensity (40 to 45 mg/m2/wk) of oxaliplatin have been used in phase III randomized studies. They have provided significantly improved response rates and progression-free survival rates over 5-FU/FA dose-intense infusional regimens. In one of these phase III trials, continuous infusion of oxaliplatin and 5-FU/FA (FOLFOX-4), provided objective response rates of 50.7% compared with 22.3% for those receiving 5-FU alone (P = .0001). Median progression-free survival was also improved with oxaliplatin (9 months) compared with 6.2 months for those treated with 5-FU/FA alone (P = .001).6 In another randomized phase III trial comparing chronomodulated 5-FU/FA alone or preceded by a continuous infusion of oxaliplatin, patients in the oxaliplatin-

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inclusive arm exhibited a significantly higher objective response rate (53%) compared with those receiving chronomodulated 5-FU/FA alone (16%; \( P < 0.001 \)). Median progression-free survival was also improved in the oxaliplatin-containing arm compared with the 5-FU/FA-alone arm (8.7 months vs 6.1 months; \( P = 0.048 \)).

The chemotherapeutic management of cancer is often accompanied by a variety of potential side effects. Consequently, the decision to use one oxaliplatin-containing regimen over another is ultimately governed by safety and tolerability considerations together with an estimation of the therapeutic goals to be achieved. Therefore, a precise knowledge of the safety profile of oxaliplatin is essential.

**TOXICITIES ASSOCIATED WITH OXALIPLATIN THERAPY**

During the course of oxaliplatin clinical trials, the adverse events most often cited were hematologic toxicity (rarely exceeding grade 3), gastrointestinal (GI) tract toxicity manifesting as nausea, vomiting, diarrhea, and mucositis, and a neurologic toxicity unlike that observed with other platinum derivatives. In none of these trials was nephrotoxicity reported. This permitted the administration of oxaliplatin without pre- or post-infusion hydration.

**Hematologic Toxicity**

Anemia, neutropenia, and thrombocytopenia have been reported sporadically at the highest dose levels of oxaliplatin explored in phase I clinical trials. In controlled trials, however, the incidence of anemia was often similar in both the oxaliplatin and control groups, suggesting that the condition is probably a manifestation of the underlying disease state. Neutropenia was low and manageable with grade 3/4 toxicity occurring in only 5% of patients in study groups evaluating oxaliplatin alone, but was more frequent in ox-
aliplatin-treated groups that included combination therapy. This was particularly evident with the FOLFOX-4 regimen (Table 1). Although this effect could be explained in part by pharmacokinetic interactions of oxaliplatin with 5-FU, resulting in increased 5-FU clearance, recent studies indicate that oxaliplatin does not affect 5-FU pharmacokinetics.

In the phase III clinical trial that used the FOLFOX-4 regimen, grade 3/4 neutropenia occurred in 41.7% of patients in the oxaliplatin plus 5-FU/FA combination arm compared with 5.3% in the control arm (Table 2). Neutropenia also occurred more often in this continuous-infusion trial than in the phase III trial that used chronomodulated 5-FU/FA infusion where only 2% of patients experienced grade 3/4 events. No oxaliplatin dose effect was observed in any of the trials surveyed and the incidence of neutropenia was comparable in pretreated and chemotherapy-naive patients.

Thrombocytopenia is a rare event sometimes observed after multiple cycles of therapy. It most often occurs as a grade 1 or 2 event, although a few patients may experience higher grades of toxicity that may lead to therapy delays. In the recently reported phase III trials, grade 3/4 thrombocytope-
nia occurred more often in the continuous-infusion trial than in the trial using chronomodulated administration of 5-FU/FA (Table 2). Other controlled studies using continuous-infusion regimens where patients served as their own control confirm this effect (Table 2) and support the notion that 5-FU metabolism is dependent on the circadian variations in dihydropyrimidine dehydrogenase activity.19,20

In phase III trials, few patients experienced febrile neutropenia (< 1%) and those with grade 3/4 neutropenia responded well to dose modification.6

**Gastrointestinal Toxicities**

Nausea and vomiting, a common occurrence resulting from the administration of many chemotherapeutic agents, is usually mild-to-moderate with oxaliplatin and readily controlled with prophylactic administration of standard antiemetics from the family of 5-HT3 receptor antagonists.

Grade 1/2 diarrhea has been reported in patients with advanced colorectal cancer treated with oxaliplatin monotherapy.11,21 Because 5-FU therapy is also a major cause of GI toxicity, the minor pharmacodynamic interactions between oxaliplatin and 5-FU also tend to enhance 5-FU-related GI tract toxicity.

A comparison of oxaliplatin monotherapy and combination therapy data from recently reported phase III trials6,9 shows that 5-FU contributes significantly more to GI toxicity than does single-agent oxaliplatin. Furthermore, the modest increase in 5-FU–related GI tract toxicities caused by oxaliplatin is usually less than additive in patients treated with the combination (Table 3). The main manifestation of GI toxicity, diarrhea, is usually higher with protracted continuous infusion or with very high infusional doses. However GI tract toxicity rarely causes discontinuation of treatment. In a study of pooled phase II data, only three of 682 patients surveyed (0.4%) discontinued therapy for this reason.22

In practice, prophylaxis is not required and oxaliplatin dose should only be reduced in subsequent cycles if diarrhea becomes severe. If excessive diarrhea occurs during protracted continuous infusion or with high infusional doses, the oxaliplatin dose should also be appropriately reduced. Incidental diarrhea is usually easily managed during oxaliplatin plus 5-FU therapy.

**Renal Function**

The phase I clinical trials demonstrated the absence of nephrotoxicity,15 even at the highest dose levels.6 This finding was confirmed in subsequent trials, including the recently completed phase III trials. In these studies, the incidence of abnormal renal function rarely exceeded 5% and was comparable in both the oxaliplatin-treated groups and the control groups.7,23 These were related to previous therapy or disease-associated

| Table 2. Hematologic Toxicities in Chemotherapy-Naive† and Previously Treated Patients‡ With Colorectal Cancer Treated With Oxaliplatin |
|---|---|---|---|---|---|
| Study Regimen | Anemia Grade 1/2 | Anemia Grade 3/4 | Neutropenia Grade 1/2 | Neutropenia Grade 3/4 | Thrombocytopenia Grade 1/2 | Thrombocytopenia Grade 3/4 |
| Phase III Study*(FOLFOX4)6 | 5-FU/FA | 78.9% | 2.5% | 24.9% | 5.3% | 28.9% | 0.5% |
| (Chrono)3,22 | 5-FU/FA + LOHP | 83.3% | 3.3% | 28.6% | 41.7% | 73.7% | 2.5% |
| Phase III L-LOHP | 5-FU daily bolus × 5d + | 75.7% | 4.3% | 35.7% | 20.0% | 55.7% | 7.8% |
| Dose Intensity† | LOHP 130 mg/m² | 87.7% | 3.5% | 15.8% | 5.3% | 40.4% | 0% |
| (Intrapatient control) | 5-FU qw LOHP 85 mg/m² | 78.9% | 5.3% | 21.1% | 33.3% | 71.9% | 7% |
| Phase III 5-FU dose Intensity† | 5-FU 0.4/0.6 LOHP 85 mg/m² | 62.5% | 0% | 37.5% | 12.5% | 62.5% | 7.5% |
| (Intrapatient Control) | 5-FU 1.5 LOHP 85 mg/m² | 78.9% | 5.3% | 21.1% | 33.3% | 71.9% | 7% |

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conditions that affect the patient’s renal functions rather than an effect of therapy. When oxaliplatin was administered at full dose without hydration to 49 patients with moderately or severely impaired renal function, no increases in either renal dysfunction or other adverse events were reported. The pharmacokinetics of oxaliplatin in patients with normal and impaired creatinine clearance value (median creatinine clearance: 70.5 mL/min and 42 mL/min, respectively) have been compared. Following the administration of a maximum tolerated dose of oxaliplatin (130 mg/m² as a 2-hour infusion without hydration), platinum binding to plasma proteins and red blood cells was rapid and extensive. Neither the mean total plasma concentration, the ultrafilterable plasma concentration, nor the maximal red blood cell platinum content differed significantly between the two patient groups. The plasma clearance of both total and free platinum, as well as the area under the curve of the free platinum fraction, correlated with the calculated creatinine clearance. In all instances, baseline renal function was inversely correlated with free drug plasma availability and directly correlated with plasma platinum clearance. None of these pharmacokinetic features influenced the characteristics of the toxicities reported in either group of patients. These results suggest that oxaliplatin can be administered equally safely to both normal and moderately renally impaired patients at recommended doses without adjustments or hydration as is mandatory with cisplatin.

Hepatotoxicity

Metabolic studies have shown that nearly half of administered oxaliplatin is recovered in the urine within 3 days of administration, with little excretion in the feces. This suggests that oxaliplatin is not metabolized nor excreted hepatically to any significant extent. A recent meta-analysis investigating the relationship between ultrafilterable platinum clearance and hepatic function showed no statistically significant differences in platinum clearance between patients with normal alanine aminotransferase (ALT) values (2 to 47 U/L) and patients with elevated ALT values (48 to 126 U/L; \( P = .507 \)). This result suggests little effect of hepatic function on platinum disposition. In practice, minor hepatic dysfunction does not warrant oxaliplatin dose modification or reduction.

Neurotoxicity

Neurotoxicity is inherent to all platinum-containing antineoplastic agents. It is cumulative with cisplatin and is not observed with carboplatin, only because hematologic toxicity is dose limiting with this agent. Among the third generation platinum derivatives, the development of tetraplatin (ormaplatin; trans-d,l-1,2-diaminocyclohexane tetrachloroplatinum [intravenous]) was abandoned...

| Table 3. Gastrointestinal Toxicities Experienced by Patients With Colorectal Cancer Treated With Oxaliplatin-Containing Regimen |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Toxicity        | Single-Agent Oxaliplatin | Single-Agent 5-FU (Inf) | Single-Agent 5-FU (Chrono) | S-FU/LOHP Combo (Inf) | S-FU/L-OHP Combo (Chrono) |
| Grade 1/2       | Grade 3/4       | Grade 1/2       | Grade 3/4       | Grade 1/2       | Grade 3/4       | Grade 1/2       | Grade 3/4       |
| Vomiting        |                  |                  |                  |                  |                  |                  |
| Becouarn et al  | 52.6%           | 7.9%            | 27.4%           | 2.0%            | 62%            | 2%             | 63.6%           | 25.3%           |
| De Gramont et al |                |                  |                  |                  |                  |                  |
| Giachetti et al |                  |                  |                  |                  |                  |                  |
| Mucositis       |                  |                  |                  |                  |                  |                  |
| Becouarn et al  | 0%              | 2.6%            | 34.1%           | 1.5%            | 55%            | 4%             | 51.5%           | 10.1%           |
| De Gramont et al |                |                  |                  |                  |                  |                  |
| Giachetti et al |                  |                  |                  |                  |                  |                  |
| Diarrhea        |                  |                  |                  |                  |                  |                  |
| Becouarn et al  | 39.5%           | 2.6%            | 38.5%           | 5.3%            | 45%            | 5%             | 42.5%           | 43.4%           |
| De Gramont et al |                |                  |                  |                  |                  |                  |
| Giachetti et al |                  |                  |                  |                  |                  |                  |
because of severe motor and sensory peripheral neuropathy at low cumulative doses.\textsuperscript{27,28} The more satisfactory safety profile of oxaliplatin may result from a different mode of biotransformation following infusion. Preclinical studies in rodents have shown that both oxaliplatin and tetraplatin are transformed into DACH-platinum dichloride, 1, 2-DACH-platinum dicysteinate, 1,2-DACH-platinum diglutathionate, and 1,2-DACH-platinum monoglutathionate, and 1,2-DACH-platinum methionine. Red blood cell cytosol contains only thiol derivatives and free diaminocyclohexane, whereas plasma contains all those listed. However, upon infusion, oxaliplatin remains unchanged for the most part in plasma, whereas 1,2-DACH-platinum dichloride is the major plasma metabolite associated from tetraplatin infusion. In a neurite outgrowth assay, 1,2-DACH platinum dichloride was 3.8-fold more neurotoxic than oxaliplatin and 1.5-fold more neurotoxic than tetraplatin.\textsuperscript{29} Limited results suggest that 1,2-DACH platinum monochloride is a major biotransformation product of oxaliplatin in humans, but its neurotoxicity has not been evaluated.\textsuperscript{30} These results may explain the different clinical neurotoxicity profiles observed with oxaliplatin and tetraplatin and suggest that the toxicity and efficacy of DACH-platinum derivatives is strongly dependent on biotransformation, biodistribution, and intracellular activation of the agent under consideration.

The occurrence of a dose-limiting neurotoxicity with unique clinical characteristics was noted during the first phase 1 clinical trial of oxaliplatin in which rapid intrapatient dose escalation and rapid bolus intravenous administration were part of the trial design.\textsuperscript{15} These effects were confirmed by Extra et al\textsuperscript{36} who used longer intravenous infusions (30 minutes to 2 hours). The symptoms reported can be separated into two distinct categories: an acute sensory disturbance with a rapid onset of hours to days following treatment, and a late onset cumulative sensory neuropathy that occurs after several cycles of therapy. Because of the unusual toxicity observed with oxaliplatin, a specific oxaliplatin neurotoxicity scale has been developed (Table 4; see also Gamelin et al elsewhere in this supplement).

In most studies, neurotoxicity evaluated on the oxaliplatin-specific neurotoxicity scale was mostly confined to grade 1 or 2 (Table 5). In the phase III trial of oxaliplatin plus 5-FU/FA versus 5-FU/FA alone,\textsuperscript{6} neurotoxicity (all grades) was significantly...
higher in the oxaliplatin group (68%) than in the 5-FU/FA alone arm (12%). In the oxaliplatin arm, 18% experienced grade 3 events. Median time to recovery from grade 3 neurotoxicity was 13 weeks. Cold-related dysesthesia occurred in 67.5% of patients, with 22% reporting pharyngolaryngeal dysesthesia. Paresthesia without pain occurred in 65.1% or patients, and paresthesia with pain was reported in 10.5%. In the phase III trial with chronomodulated 5-FU/FA, 13% of patients in the oxaliplatin arm experienced grade 3 neurosensory side effects with functional impairment, compared with 0% in the control arm. Neurosensory side effects are unrelated to the dose of oxaliplatin and occur more frequently in previously treated patients. In some of these studies, patients have been treated with oxaliplatin for as long as 18 months (cumulative oxaliplatin dose > 3,000 mg/m²) with no signs of grade 3 neuropathy.

At high cumulative doses of more than 1,000 mg/m², incidences of central neurotoxicity, particularly Lhermitte’s sign, have been observed in a small number of patients (3.3% in phase III trials) with resolution occurring a few weeks after discontinuation of therapy.

After several years of follow-up of hundreds of patients, it has been shown that, unlike cisplatin, oxaliplatin rarely causes worsening of symptoms after discontinuation. Furthermore, grade 2 and 3 peripheral neuropathy is consistently reversible, with partial to complete resolution of symptoms. In the recent phase III trials by de Gramont et al, reversibility of sensory neuropathy has been achieved in approximately three quarters of patients with grade 3 events (Fig 2).

In the most recent phase III trials, symptoms of chronic cumulative neuropathy have been minimized with a biweekly administration of 85 mg/m² oxaliplatin over a 2-hour infusion. No dose reductions were necessary, but some dose delays from biweekly to triweekly administration were implemented. With higher frequency schedules that use lower doses of oxaliplatin (50 mg/m² on a weekly basis), a shorter infusion time of 1 hour has been used successfully. Conversely, to reduce neurologic symptoms, oxaliplatin infusion has been extended for as long as 6 hours or a 4- to 5-day continuous intravenous flat rate or chronomodulated intravenous administration.

The recently completed phase III trials show that an acceptable neurologic outcome can be achieved with appropriate management strategies with the oxaliplatin plus 5-FU/FA combination. They highlight the favorable safety profile of oxaliplatin compared with neurotoxic agents such as cisplatin and the taxanes.
Ototoxicity

Because both cisplatin and, to a lesser extent, carboplatin are ototoxic, the potential ototoxicity of oxaliplatin has been evaluated. Thirty-two patients with advanced squamous cell carcinoma of the upper respiratory tract were randomized to cisplatin (100 mg/m² triweekly plus 1,000 mg/m² 5-FU each day of the first 4 days of each cycle) or oxaliplatin (130 mg/m²). Auditory capacity was evaluated to detect by pure tone audiometry at frequencies of 2,000, 4,000 and 6,000 Hz and high frequency audiometry from 8,000 to 18,000 Hz. The likelihood of ototoxicity was defined as auditory loss greater than 15 db in a single ear in one test. Repeated evidence of loss over several auditory tests was classified as definite auditory loss. An evaluation of auditory brain stem evoked responses and a speech discrimination test were also administered. Of 14 patients evaluable in the cisplatin group, 11 (78.6%) showed some signs of ototoxicity, but of the 15 evaluable patients in the oxaliplatin group, only 4 (26.7%) did so, all related to presbyacusis. In addition, whereas patients treated with oxaliplatin showed minor levels of toxicity, those who received cisplatin exhibited more severe symptoms.34 This study showed that the potential for oxaliplatin-mediated ototoxicity at the recommended dose is low.

Other Adverse Events

Allergic reactions have been reported, as with cisplatin, on rare occasions (usually 5% of patients or less) and often in patients who had been pretreated with cisplatin. The symptoms can usually be controlled with antihistamines or glucocorticoids after discontinuance of treatment. When this course of action may be beneficial, resumption of treatment should only be undertaken in the absence of alternative therapy and after informed consent from the patient. Prophylactic therapy should be administered and the patient should be carefully monitored.

A major benefit of oxaliplatin therapy is the rare incidence of alopecia, even in combination with 5-FU. This is significant because a recent survey of cancer patients indicates that alopecia is their second most important concern regarding therapy side effects.

CONCLUSIONS

To date, oxaliplatin has proven to be a safe and effective treatment for colorectal cancer. Its synergistic properties with 5-FU have resulted in over 50% objective response rates in patients newly diagnosed with advanced colorectal cancer.6-9 Treatment with oxaliplatin is characterized by a minimal incidence of life-threatening toxicities. The use of oxaliplatin for up to 6 months in either schedule at the recommended dose intensity is both safe and feasible, as experience in many hundreds of patients with colorectal cancer has shown. Alopecia, a side effect of many chemotherapies much-feared by patients, is rarely seen, and nausea and vomiting are easily controlled with prophylactic antiemetics. The enhancement of 5-FU–induced hematologic toxicity rarely results in grade 3/4 events and is usually not cause for postponement or discontinuation of therapy. Thrombocytopenia occurs after many cycles of therapy and usually in patients who have been heavily pretreated. Unlike cisplatin, oxaliplatin is not nephrotoxic and does not require concurrent hydration. The dose-limiting toxicity of oxaliplatin is a peculiar type of sensory peripheral neuropathy that occurs in 50% of patients after protracted dosing and is reversible in over 80% of those who are affected. Its use above the 700 to 800 mg/m² cumulative dose level should be carefully clinically monitored, and the adequate management of neurotoxicity by treatment delay and/or dose adaptation may allow prolonged therapy. With appropriate awareness from patients and health care providers, the acute manifestations of cold-onset dysesthesias and other adverse events associated with oxaliplatin therapy can be properly managed. The remarkable safety profile and activity of oxaliplatin have fostered its introduction as a first-line therapy for the treatment of advanced colorectal cancer. They also suggest its use for earlier stages of the disease, in new combination therapies, and for new indications. The investigation of its activity against tumors with increasing resistance to cisplatin or carboplatin is also warranted.

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