

# Hypersensitivity to Oxaliplatin: An Investigation of Incidence and Risk Factors, and Literature Review

Brian H. Kim<sup>a</sup> Thomas Bradley<sup>a</sup> Julia Tai<sup>b</sup> Daniel R. Budman<sup>a</sup>

<sup>a</sup>Monter Cancer Center, North Shore – LIJ Health System, New York University School of Medicine, Lake Success, N.Y., and <sup>b</sup>Biostatistics Unit, The Feinstein Institute for Medical Research, Manhasset, N.Y., USA

## Key Words

Oxaliplatin · Hypersensitivity · Neurotoxicity · Myelosuppression

## Abstract

**Background:** Hypersensitivity is a well-known complication of the platinum agents cisplatin and carboplatin. Although hypersensitivity to oxaliplatin has been noted, the incidence varies significantly in reports. Risk factors for developing reactions specifically to oxaliplatin have not been evaluated. We report the 5-year incidence of hypersensitivity to oxaliplatin in our clinical program, the patient and disease characteristics associated with its occurrence, and review the literature. **Methods:** Clinical information on all patients treated with oxaliplatin between September 2002 and August 2007 was retrospectively reviewed. Data from patients who experienced hypersensitivity were compared to patients treated with this agent who did not. Risk factors investigated included age, sex, diagnosis, disease stage, presence of preexisting allergies, chemotherapy received, and use of oxaliplatin in front-line versus salvage therapy. **Results:** 247 patients received oxaliplatin, with 29 experiencing hypersensitivity, for an incidence of 11.7% (95% CI 7.7–15.8). Grade 3/4 events occurred in 1.6%. Hypersensitivity was associated with younger mean age ( $54.9 \pm 12.5$  vs.  $60.4 \pm 12.4$  years with reactions vs. those without,  $p = 0.02$ ), female gender (17.2% of

females vs. 6.4% of males,  $p = 0.01$ ) and with use of oxaliplatin as salvage therapy (23.9% second-line or higher vs. 9.1% front-line,  $p = 0.01$ ). **Conclusions:** Our data demonstrate an incidence of hypersensitivity to oxaliplatin of 11.7%, with grade 3/4 events in 1.6%. As use of this agent becomes more widespread, increased vigilance for this potentially serious complication should be high, especially amongst younger patients, females, and with the use of oxaliplatin as salvage therapy; three newly recognized potential risk factors.

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## Introduction

Oxaliplatin is a third-generation platinum agent with a 1,2-diaminocyclohexane carrier ligand and an oxalate leaving group [1]. Its anti-neoplastic effects occur via generation of DNA adducts onto intra- or interstrand guanine residues, which lead to DNA kinks and strand breaks, as well as inhibition of DNA polymerase and DNA synthesis. This, in turn, leads to cell cycle arrest and apoptosis [2]. Oxaliplatin has efficacy against colorectal

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cancers and is FDA-approved in the United States for this use, first in 2002 for the treatment of refractory metastatic disease and later in 2004 for front-line therapy in both metastatic and adjuvant settings. It has additionally shown activity in a wide variety of tumor types, including pancreatic, biliary, gastroesophageal, and gynecologic malignancies, amongst others [3].

The major adverse events associated with oxaliplatin consist of neurological toxicity, myelosuppression, nausea, vomiting, and diarrhea, of which neurotoxicity is the most prominent and the usual dose-limiting factor [4–6]. These effects typically occur well after the treatment infusion has been completed. Infusion reactions to platinum agents have also been well described [7], and analogous to cisplatin and carboplatin, oxaliplatin has been increasingly recognized to cause hypersensitivity reactions. Published information has noted a marked variation in the rate of this side effect. Additionally, factors that might place individual patients at increased risk of hypersensitivity to any of the platinum agents, and to oxaliplatin in particular, have not heretofore been investigated in depth. Here we report the 5-year experience with oxaliplatin hypersensitivity at a single institution and review the literature with regard to risk factors.

## Patients and Methods

### Patient Selection and Demographics

Approval for this retrospective study was obtained from the institutional review board. All patients treated with oxaliplatin at the Don Monti Division of Medical Oncology at North Shore University Hospital over a 5-year period from September 2002 through August 2007 had their clinical courses reviewed. These patients received treatment for a variety of malignant conditions, the vast majority of which were colorectal carcinoma. Hypersensitivity was classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v3.0, <http://ctep.gov>). Patients with hypersensitivity reactions were further analyzed by age, gender, cancer diagnosis, disease stage, presence of preexisting allergies, treatment regimen, and treatment line of therapy. These characteristics were compared to the cohort of patients who had received oxaliplatin without experiencing reactions. Information regarding cycle number at the time of occurrence, use of premedications, time elapsed before onset of the reaction, interventions taken, and patient outcomes was also recorded.

### Statistical Analysis

Statistical analysis was carried out using the t test to determine if age was associated with hypersensitivity. All other factors were evaluated using Fisher's exact test. Results were considered significant when  $p < 0.05$ . Multiple logistic regression analysis was then used to determine which variables, in combination, jointly predicted hypersensitivity. All variables with a  $p$  value of  $<0.1$  were considered candidates for multiple logistic regression.

**Table 1.** Baseline characteristics of all patients treated with oxaliplatin

| Characteristic                   | n         | %             |
|----------------------------------|-----------|---------------|
| Age, years                       | 60 (mean) | 24–89 (range) |
| Sex                              |           |               |
| Male                             | 125       | 51            |
| Female                           | 122       | 49            |
| Allergies <sup>1</sup>           |           |               |
| None                             | 175       | 70            |
| Medication                       | 59        | 24            |
| Seafood                          | 6         | 2             |
| Iodide/intravenous dye           | 4         | 2             |
| Tape                             | 2         | 1             |
| Diagnosis                        |           |               |
| Colon                            | 151       | 61            |
| Rectum                           | 42        | 17            |
| Appendix                         | 14        | 6             |
| Pancreas                         | 24        | 10            |
| Gallbladder/biliary              | 8         | 3             |
| Other <sup>2</sup>               | 8         | 3             |
| Disease stage <sup>1</sup>       |           |               |
| II, III                          | 100       | 41            |
| IV                               | 145       | 59            |
| Treatment regimen <sup>1,3</sup> |           |               |
| FOLFOX                           | 115       | 46            |
| FOLFOX-bevacizumab               | 44        | 18            |
| FLOX                             | 24        | 9             |
| XELOX                            | 23        | 9             |
| XELOX-bevacizumab                | 8         | 3             |
| Oxaliplatin-gemcitabine          | 29        | 12            |
| Other <sup>4</sup>               | 7         | 3             |
| Line of therapy                  |           |               |
| Initial                          | 199       | 81            |
| Second or higher                 | 48        | 19            |

<sup>1</sup> Data missing regarding allergies and treatment regimen in 1 patient, and disease stage in 2 patients.

<sup>2</sup> Includes gastric, non-Hodgkin's lymphoma, ovarian, small intestine, and unknown primary.

<sup>3</sup> Total exceeds 247 as a few patients received multiple different regimens.

<sup>4</sup> Includes: FOLFOX = 5-fluorouracil-oxaliplatin with and without bevacizumab; oxaliplatin-gemcitabine-bevacizumab; oxaliplatin-docetaxel; XELOX = cetuximab and oxaliplatin with and without bevacizumab; FLOX = bolus 5-fluorouracil with oxaliplatin, and single-agent oxaliplatin.

## Results

The demographics of all patients who received oxaliplatin are shown in table 1. These patients were balanced between genders, with a mean age of 60 years. Nearly three quarters had no prior history of allergic reactions. Amongst

**Table 2.** Hypersensitivity reactions to oxaliplatin 2002–2007

|                             |                    |
|-----------------------------|--------------------|
| Total patients              | 247                |
| Hypersensitivity reactions  |                    |
| Total                       | 29 (11.7%)         |
| Grade 3 events              | 4 (1.6%)           |
| Grade 4 events              | 0                  |
| Time to reaction, min       |                    |
| Median (range)              | 70 (10 min to 4 h) |
| Cycle number at event       |                    |
| Median (range)              | 7 (1–11)           |
| Premedications <sup>1</sup> |                    |
| Dexamethasone               | 28                 |
| Hydrocortisone              | 1                  |
| Antihistamines              | 3                  |
| None                        | 1                  |

<sup>1</sup> Twenty-eight patients received dexamethasone; 1 patient received both dexamethasone and hydrocortisone; 3 patients received antihistamines in addition to dexamethasone; 1 patient received no premedications.

**Table 3.** Age of patients with and without hypersensitivity

|                 | Patients with hypersensitivity (n = 29) | Patients without hypersensitivity (n = 218) | p value |
|-----------------|-----------------------------------------|---------------------------------------------|---------|
| Mean age, years | 54.9 ± 12.5                             | 60.4 ± 12.4                                 | 0.0242  |

preexisting allergies, over 80% were to medications, with the remainder consisting of seafood, iodide/i.v. contrast dye, and tape. None of these allergies were to platinum agents. Seventy-eight percent of patients received treatment for colorectal carcinoma with the majority of these in the metastatic setting. Treatment regimens for colorectal and appendiceal tumors included infusion 5-fluorouracil with oxaliplatin, with or without bevacizumab, capecitabine with oxaliplatin, also with or without bevacizumab, and bolus 5-fluorouracil with oxaliplatin. Patients with pancreatic or biliary malignancies received oxaliplatin in combination with gemcitabine. Other oxaliplatin-containing regimens were given as appropriate for the tumor type. Eighty-one percent of patients were being treated with their initial chemotherapy regimen.

During this 5-year period, 247 patients received oxaliplatin. Hypersensitivity reactions occurred in 29 patients (table 2), resulting in an incidence of 11.7% (95% CI 7.7–

15.8) of all treated patients. Of the patients who experienced events, 5 patients were rechallenged with oxaliplatin. Three of 5 patients had second reactions, producing a total of 32 incidents in 29 patients. An aggregate of 1,814 doses of oxaliplatin was administered to our 247 patients, for an overall frequency of hypersensitivity reactions in 1.8% of all infusions. The most common events were flushing (15 patients), urticaria (15 patients), and dyspnea without bronchospasm (7 patients). Grade 3 events included symptomatic bronchospasm in 2 patients, hypotension in 1 patient, and angioedema in 1 patient, for an incidence of 1.6% of all patients, or 0.22% of all infusions. Two of these patients experienced symptomatic bronchospasm; 1 developed angioedema in the presence of subjective dyspnea without bronchospasm, and 1 became hypotensive also with subjective dyspnea without bronchospasm. There were no grade 4 events (i.e. anaphylaxis) and no deaths. In no case did the treating physician allow the side effects to resolve by discontinuing oxaliplatin and observation alone. Additional corticosteroids, antihistamines, oxygen, and bronchodilators were used to antagonize the reactions based upon the discretion of the treating physician. Reactions took place at a median of 7 (range 1–11) cycles of treatment (table 2). The median time to reaction after initiation of the infusion was 70 min (range 10 min to 4 h). All but 1 of these 29 patients had received pretreatment with dexamethasone, as antiemesis prophylaxis, in addition to the 5-HT<sub>3</sub> blocker of the treating physician's choice.

Events taking place after rechallenge were not associated with a greater severity of symptoms. Two patients upon rechallenge with oxaliplatin after a prior reaction also received the antihistamines diphenhydramine and famotidine as part of their premedication regimen. Both these patients suffered second events despite these additional medications. These second events occurred at the 7th and 11th exposure to oxaliplatin. Hydrocortisone was also used in addition to dexamethasone and diphenhydramine in 1 patient who had a prior history of anaphylaxis to intravenous contrast dye. This patient, receiving an oxaliplatin-based regimen for colon cancer, experienced a grade 3 event on her 7th cycle of treatment. No patient was offered a desensitization protocol.

Characteristics of those who experienced hypersensitivity reactions were similar to all patients who received oxaliplatin, with three significant differences (tables 3–5). The group of patients with reactions was younger, having a mean age of 54.9 years, compared to those without reactions, who had a mean age of 60.4 years ( $p = 0.02$ ). Females were more likely to experience hypersensitivity

**Table 4.** Characteristics of patients with hypersensitivity reactions

| Characteristic               | Patients with hypersensitivity |    | All patients | p value |
|------------------------------|--------------------------------|----|--------------|---------|
|                              | %                              | n  |              |         |
| Sex                          |                                |    |              |         |
| Male                         | 6.4                            | 8  | 125          | 0.0098  |
| Female                       | 17.2                           | 21 | 122          |         |
| Allergies                    |                                |    |              |         |
| Present                      | 14.1                           | 10 | 71           | 0.5148  |
| NKDA                         | 10.9                           | 19 | 175          |         |
| Diagnosis                    |                                |    |              |         |
| Colon                        | 13.9                           | 21 | 151          | 0.2112  |
| Rectum                       | 4.8                            | 2  | 42           |         |
| Pancreas                     | 4.2                            | 1  | 24           |         |
| Others                       | 16.7                           | 5  | 30           |         |
| Disease stage                |                                |    |              |         |
| II, III                      | 10                             | 10 | 100          | 0.5483  |
| IV                           | 13.1                           | 19 | 145          |         |
| Line of therapy <sup>1</sup> |                                |    |              |         |
| Initial                      | 9.1                            | 18 | 197          | 0.0100  |
| Second or higher             | 23.9                           | 11 | 46           |         |

<sup>1</sup> Only 1 patient with hypersensitivity receiving oxaliplatin in a salvage regimen had prior exposure to any platinum agent.  
NKDA = No known drug allergies.

events, with 17.2% of all women treated with oxaliplatin having reactions compared to only 6.4% of all men ( $p = 0.01$ ). Of the 29 patients who had events, 21 of these (72%) were women. Finally, patients receiving oxaliplatin as salvage therapy also had a greater likelihood of reactions. Although only 19% of all patients were treated with second-line or higher regimens, 38% of the group who experienced reactions were receiving treatment beyond the first line. This finding translated into a 24% incidence of hypersensitivity in patients receiving salvage therapy versus 9% in those being treated with initial therapy ( $p = 0.01$ ). Using multiple logistic regression analysis, all three factors remained statistically significant. The presence of prior allergies, disease type, disease stage, and treatment regimen were not associated with hypersensitivity.

## Discussion

Hypersensitivity is defined as an unexpected reaction that is inconsistent with a drug's usual toxicity profile, occurring during or immediately following the adminis-

**Table 5.** Treatment regimen of patients with hypersensitivity reactions

| Treatment regimen                    | Patients with hypersensitivity |    | All patients | p value |
|--------------------------------------|--------------------------------|----|--------------|---------|
|                                      | %                              | n  |              |         |
| FOLFOX                               |                                |    |              | 0.6828  |
| Yes                                  | 12.6                           | 20 | 159          | 0.7637  |
| No                                   | 10.3                           | 9  | 87           |         |
| XELOX                                |                                |    |              |         |
| Yes                                  | 13.3                           | 4  | 30           | 1.000   |
| No                                   | 11.6                           | 25 | 216          |         |
| FLOX                                 |                                |    |              |         |
| Yes                                  | 12                             | 3  | 25           | 0.4744  |
| No                                   | 11.8                           | 26 | 221          |         |
| Any bevacizumab-containing treatment |                                |    |              |         |
| Yes                                  | 14.8                           | 8  | 54           | 0.5465  |
| No                                   | 10.9                           | 21 | 192          |         |
| Oxaliplatin-gemcitabine              |                                |    |              |         |
| Yes                                  | 6.7                            | 2  | 30           | 1.000   |
| No                                   | 12.5                           | 27 | 216          |         |
| Others                               |                                |    |              |         |
| Yes                                  | 0                              | 0  | 5            | 1.000   |
| No                                   | 12                             | 29 | 241          |         |

FOLFOX = 5-Fluorouracil infusion with oxaliplatin; XELOX = capecitabine with oxaliplatin; FLOX = 5-fluorouracil bolus with oxaliplatin.

tration of the medication [7]. Hypersensitivity reactions to a variety of agents have resulted in serious reactions and even death [7, 8]. Hypersensitivity to the platinum analogs cisplatin and carboplatin are well documented [7, 9–11]. For cisplatin, hypersensitivity reactions have been reported as 2–5% when administered as a single agent and 5–10% when used in combination regimens [9]. Carboplatin reactions have occurred with a 12–27% incidence [7, 11]. The most recent commercially approved platinum, oxaliplatin, is also recognized to be associated with this condition as well [8].

An early analysis of this subject reported a cumulative incidence of 7 events in 1,278 patients, or 0.55% [12]. More recent series from multiple institutions have documented a significantly higher incidence (table 6), reporting frequencies of hypersensitivity between 8 and 19% [3, 13–17]. In aggregate, these later studies identified 104 events amongst 780 patients treated with oxaliplatin-containing regimens, for an incidence of 13%. The result of our analysis, the largest single-institution patient set yet recorded, is consistent with this result, with an observed 11.7% rate of reactions. The MOSAIC trial, a large randomized

**Table 6.** Incidence of hypersensitivity reactions in recent analyses

| Study                 | Events/<br>sample size | % (All)                   | Grade<br>3–4 |
|-----------------------|------------------------|---------------------------|--------------|
| Dold et al. [13]      | 19/235                 | 8                         | NR           |
| Brandi et al. [14]    | 17/124                 | 14                        | NR           |
| Lenz et al. [15]      | 4/25                   | 16                        | NR           |
| Hsuen Lim et al. [16] | 5/47                   | 11                        | NR           |
| Gowda et al. [3]      | 32/169                 | 19                        | <1           |
| Siu et al. [17]       | 27/180                 | 15                        | 2.2          |
| Total                 | 104/780                | 13                        |              |
| Present study         | 29/247                 | 11.7<br>(95% CI 7.7–15.8) | 1.6          |
| Total                 | 133/1,028              | 13                        |              |

NR = Not reported.

multi-institution randomized trial in which over 1,100 patients received 5-fluorouracil with oxaliplatin for colorectal cancer in the adjuvant setting, noted a similar 10.3% incidence of hypersensitivity reactions [4]. Our observed frequency of grade 3–4 events also correlates well with prior reports [8]. As a consequence, the true incidence of these events is in the range of 10–13% of all patients receiving oxaliplatin.

Few investigations have attempted to identify potential risk factors for hypersensitivity to the platinum compounds. Lee et al. [8] analyzed the possible association between oxaliplatin-induced anaphylaxis and both the site and the number of metastases, with no significant association identified. Escalante et al. [18], in abstract form, described risk factors common to all chemotherapeutic agents and monoclonal antibodies, including carboplatin and oxaliplatin, that were associated with immediate adverse drug reactions observed at their center. These factors included existing allergies to medications, previous immediate drug reactions, previous reactions to iodide, seafood allergies, allergic rhinitis, urticaria, and asthma [18]. Markman et al. [19] found a statistically significant increased risk in individuals receiving carboplatin who reported a prior episode of hypersensitivity to either drugs or environmental agents. In contrast, however, our analysis demonstrated none of these associations.

We did observe a greater likelihood of hypersensitivity in patients treated with oxaliplatin as salvage therapy. Nearly 24% of those treated with this agent beyond the first-line had reactions, compared to only 9% of patients

**Table 7.** Hypersensitivity reactions by gender

| Study                        | Female   | Male     |
|------------------------------|----------|----------|
| Case reports                 |          |          |
| Tournigand et al. [35]       | 2        | 3        |
| Medioni et al. [24]          |          | 1        |
| Larzilliere et al. [37]      |          | 1        |
| Alliot et al. [38]           |          | 1        |
| Schull et al. [39]           |          | 1        |
| Stahl et al. [44]            |          | 2        |
| Santini et al. [25]          |          | 1        |
| Thomas et al. [12]           | 2        | 1        |
| Garufi et al. [50]           | 5        | 1        |
| Bhargava et al. [43]         | 1        |          |
| Gammon et al. [29]           | 1        |          |
| Lim et al. [42]              |          | 1        |
| Gonzalez-Mahave et al. [32]  | 1        | 1        |
| Mis et al. [41]              | 1        |          |
| Ng [40]                      | 2        |          |
| Herrero et al. [33]          | 2        | 3        |
| Edmondson et al. [30]        |          | 1        |
| Sagawa et al. [36]           |          | 1        |
| Rosique-Robles et al. [51]   | 1        |          |
| Saif et al. [45]             | 1        |          |
| Kitada et al. [23]           | 1        |          |
| Retrospective analyses       |          |          |
| Dold et al. [13]             | 11       | 8        |
| Hsuen Lim et al. [16]        | 4        | 1        |
| Maindault-Goebel et al. [20] | 30       | 12       |
| Present study                | 21       | 8        |
| Total                        | 84 (64%) | 48 (36%) |

being treated with their initial regimen. Previous reports have not formally investigated this factor. Maindault-Goebel et al. [20] offer the contrasting statement that the line of therapy did not seem to predict reactions, but do not provide an analysis of the data used to reach this conclusion. It is unclear why patients treated with salvage therapy should be more likely to experience hypersensitivity reactions. Prior exposure to cisplatin or carboplatin might be considered a possible cause, but this is not evidenced in our data as only 1 patient who experienced hypersensitivity had had prior exposure to a platinum agent. One may speculate that as yet unknown pathophysiological mechanisms underlying hypersensitivity to oxaliplatin may be responsible.

In our study, the use of pretreatment medication with dexamethasone, at a dose used for anti-emesis, had no protective effect on the development of hypersensitivity. This observation is consistent with the published literature. Antihistamines and prolongation of the infusion

time of oxaliplatin had inconsistent effects on the subsequent development of reactions. Desensitization was not employed in this patient cohort at our center.

The group of patients who had hypersensitivity reactions was also younger than the group without reactions, 54.9 and 60.4 years, respectively. This characteristic has also never before been noted in prior reports. However, though statistically significant, the *p* value for this association is not as robust as with the other two identified variables. Additionally, our entire population, with a mean age of 60 years, was younger than the population of all patients newly diagnosed with colorectal, pancreatic, gallbladder, and biliary cancers in the United States, each of which has a median age above 70 years [21]. This difference may reflect referral patterns to a tertiary institution. Thus, the association of age as a risk factor for hypersensitivity to oxaliplatin is hypothesis-generating and worthy of further study.

We also report a gender-specific difference in incidence, with female patients more likely to have reactions. Women comprised 72% of patients in this study who experienced hypersensitivity, producing a 17% incidence of hypersensitivity in all treated women versus just 6% in all treated men. While this distinction has never been commented on previously, an inspection of those studies that reported patient gender shows this to be a consistent finding (table 7). The reasons for this increased risk amongst females are not known, but this finding is consistent with a greater incidence of anaphylaxis to multiple agents that is known to occur among women compared to men [22]. This finding may possibly relate to immunologic mechanisms, which have been proposed as part of the underlying pathophysiology. A discussion of these mechanisms is beyond the scope of this article, but has been reviewed elsewhere [15, 23–27]. Alternatively, an association between female gender and younger age implicates a possible role for hormonal influences, a relationship that has never before been studied.

The only factor in earlier studies noted repeatedly to increase risk is prior exposure to platinum agents, with risk increasing with continued cycles of therapy. This finding is best documented for carboplatin [10, 28]. Markman et al. [10] reported a 27% incidence of hypersensitivity reactions to carboplatin with seven or more courses of therapy compared to 1% in patients receiving six cycles or less. Similarly, Polyzos et al. [28] observed a 16% rate of reactions to carboplatin, which only occurred after a minimum of five cycles of treatment. Previous reports of hypersensitivity to oxaliplatin have described comparable results, with the incidents generally occurring after

four to six administrations [27, 29]. Our analysis is consistent with this finding, with reactions taking place at a median of the seventh cycle. Of note, however, reactions may occur with any treatment cycle, with both early [3, 13, 16, 17, 20, 30] and late toxicity [10, 31] documented. Also, reactions in our patients were observed with oxaliplatin use in salvage regimens after prior therapy with other oxaliplatin-based regimens. Others have described this pattern as well [15, 29, 32, 33], and is important as chemotherapy holidays are increasingly employed based upon the OPTIMOX 1 study [34].

Observed time to reaction following initiation of the infusion varies widely in our experience and in the literature. At a median of 70 min, and an upper limit beyond 4 h in 1 individual, our patients' events occurred later than those in most published studies, which noted reactions usually within the first 30 min [29, 32, 35–43]. However, other investigators have also observed episodes at 1–2 h [14, 25, 30, 33, 44, 45], and recently a patient has been described who experienced reactions over 20 h after completing her oxaliplatin infusion [46].

Finally, it is noteworthy that no treatment regimen was associated with an increased risk of hypersensitivity. In particular, the anti-VEGF monoclonal antibody bevacizumab was not associated with these reactions when given with any of five different combination chemotherapy regimens. This finding is important as combinations of oxaliplatin with bevacizumab are being increasingly investigated in gastrointestinal malignancies. The anti-EGFR antibodies panitumumab and, especially, cetuximab are well known to be associated with infusion reactions [47–49]. Whether the co-administration of these agents with oxaliplatin might increase the incidence of hypersensitivity reactions is another point of interest. In this investigation, the patients treated with either agent were too few to be able to comment on this possible association.

## Conclusions

Hypersensitivity is a significant potential adverse reaction to oxaliplatin, occurring in approximately 12% of cases, with grade 3/4 events in 1–2%. Given this frequency, and the potential severity and adverse outcomes, identification of patient risk factors for the development of these reactions may be of possible therapeutic benefit. In this analysis, younger patients, females, and patients receiving oxaliplatin in salvage regimens had a greater predilection for occurrence. Events typically take place after

sensitization with at least 4 treatment cycles, but can occur both late after heavy exposure and early within the first few cycles. Re-introduction of oxaliplatin following treatment holidays or other lines of therapy may also be associated with early events. Reactions occur at a range of times following initiation of the infusion, classically within the first 30 min but also frequently delayed for

hours. Re-introduction of oxaliplatin following treatment holidays or other lines of therapy may also be associated with the rapid appearance of hypersensitivity reactions. As use of this agent becomes more widespread, increasing vigilance and recognition of this potentially serious complication should be high.

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