Hypersensitivity Reactions to Oxaliplatin: Incidence and Management

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Oxaliplatin (Eloxatin) is a novel platinum compound that has activity in a wide variety of tumors. Several hypersensitivity reactions distinct from laryngopharyngeal dysesthesia have been described. We retrospectively analyzed 169 consecutive patients who received oxaliplatin for esophageal or colorectal cancer between 1/1/00 and 7/31/02 and reviewed any significant adverse reactions labeled as hypersensitivity reactions. Thirty-two patients (19%) reportedly experienced hypersensitivity. Skin rash was the most common event (22 patients), occurring after a median of three infusions. Fever was seen in five patients after a median of two infusions. Five patients experienced respiratory symptoms at median infusion number 6. Ocular symptoms of lacrimation and blurring of vision were seen in two patients. Five patients experienced more than one type of reaction. Treatments prescribed for hypersensitivity were antihistamines, steroids, and topical emollients. One patient developed grade 4 hypersensitivity during cycle 6, characterized by laryngeal edema, tongue swelling, and labored breathing. This patient underwent a desensitization procedure, adapted from guidelines for carboplatin (Paraplatin) allergy. Subsequently, three cycles were administered over 6 hours and were well tolerated. However, during the fourth infusion postdesensitization, the patient developed recurrent signs of hypersensitivity. In conclusion, hypersensitivity is frequently seen with oxaliplatin, but most reactions are mild.

Oxaliplatin (Eloxatin) is a third generation platinum-containing compound complexed to 1,2-diaminocyclohexane in the trans- R,R or L configuration with an oxalate ligand as a leaving group. It forms intra- and interstrand DNA platinum adducts which inhibit DNA synthesis, induce apoptosis, and inhibit tumor cell growth and protein synthesis.[1,2] Oxaliplatin has been used as a single agent and in combination with fluorouracil (5-FU) in colorectal cancer.[3,4] It has also shown activity in various other malignancies such as advanced ovarian carcinoma, astrocytoma, breast cancer, non-Hodgkin's lymphoma, melanoma, non-small-cell lung cancer, and head and neck malignancies.[5-9] Oxaliplatin is not cross-resistant with cisplatin and carboplatin (Paraplatin) in human ovarian cell lines, both in vitro and in vivo.[10] The range of oxaliplatin toxicity varies from acute reversible sensory symptoms such as cold-sensitive dysesthesia to cumulative peripheral neurotoxicity. In general, oxaliplatin lacks nephrotoxicity and is less myelotoxic than cisplatin and carboplatin, making it an ideal candidate for combination therapy. The dose-limiting neurotoxicity is reversible within a few months of discontinuation of the drug.[11] There are few reports in the literature describing oxaliplatin hypersensitivity, unlike other platinum compounds such as cisplatin and carboplatin.[12-15] The incidence of allergic reactions to carboplatin and cisplatin is approximately 5%. [12] For oxaliplatin, the incidence of severe anaphylactic reaction is estimated to be 0.5%, whereas the incidence of other hypersensitivity reactions in clinical practice is estimated to be 12% to 13%.[13,14] These reactions are often self-limited but, as discussed below, may be unpredictable. They are rarely life-threatening.
We conducted a retrospective analysis of patients treated with oxaliplatin for gastrointestinal malignancies at Roswell Park Cancer Institute and here report the incidence, clinical features, and management of hypersensitivity reactions in this group of patients. A desensitization schedule used for one patient who experienced life-threatening hypersensitivity is also discussed. **Incidence and Management**

The objective of this investigation was to assess the incidence and management of hypersensitivity reactions to oxaliplatin. We reviewed all clinical records, including charts, case report forms, and chemotherapy infusion notes of patients enrolled in two clinical trials of oxaliplatin. These patients were treated between January 1, 2000, and July 31, 2002. Institutional review board approval was obtained for this study. All patients were treated with a combination of oxaliplatin and 5-FU. The first protocol consisted of oxaliplatin followed by a 2-day schedule of bolus 5-FU and infusional leucovorin/5-FU (FOLFOX-4) for colorectal cancer. The second protocol was for esophageal cancer, consisting of radiotherapy and infusional 5-FU along with oxaliplatin. In each instance, oxaliplatin was administered over 2 hours and preceded by dexamethasone (10 mg) and ondansetron (Zofran, 8 mg). A total of 169 patient records were reviewed. Data regarding hypersensitivity reactions to oxaliplatin were obtained from the chemotherapy records, clinic notes, and case report forms. Cold-induced symptoms, including laryngospasm and neuropathy, were excluded. The spectrum of symptoms and signs related to hypersensitivity is very broad, varying from mild cutaneous inflammation to life-threatening anaphylaxis. The following reactions were considered as probable hypersensitivity reactions: skin rash, flushing, pruritus, lacrimation, blurred vision, wheezing, chest discomfort, fever, chills, slurred speech, hypotension, and anaphylactic shock. **Overview of Data**

Among 169 patients, 32 experienced one or more hypersensitivity reactions to oxaliplatin. These data are described in Table 1. Five patients experienced more than one reaction: Three developed fever and rash, two had respiratory symptoms including wheezing—one of these patients also developed ocular irritation—and the other developed skin rash. Twenty-two patients developed erythematous, macular skin rash, which was the most common reaction. Skin rash occurred after a median of three infusions. Other skin reactions included facial flushing, palmar erythema, urticaria, and generalized pruritus. Most of these skin reactions were self-limited and treated successfully with antihistamines and/or a single dose of dexamethasone. In none of the cases was oxaliplatin discontinued due to this complication. Five of these 22 patients had a recurrence of skin reaction.

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Number of Patients</th>
<th>Median Infusion Number at First Reaction</th>
<th>Range (SD)</th>
<th>Immediate Treatment</th>
<th>Change in Planned Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>22</td>
<td>3</td>
<td>1–10 (2.40)</td>
<td>Symptomatic: antihistamines, steroids</td>
<td>Treatment continued as planned</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
<td>2</td>
<td>1–9 (3.27)</td>
<td>Symptomatic: acetaminophen</td>
<td>Treatment continued</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>7</td>
<td>6</td>
<td>1–11 (3.63)</td>
<td>Dose reduction or no intervention</td>
<td>Treatment continued with reduced dose</td>
</tr>
<tr>
<td>Ocular symptoms</td>
<td>2</td>
<td>1</td>
<td>1 (0)</td>
<td>No treatment</td>
<td>Treatment continued with reduced dose</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1</td>
<td>6</td>
<td>6 (0)</td>
<td>Symptomatic: antihistamines, steroids</td>
<td>Patient treated per desensitization protocol, developed rash on rechallenge</td>
</tr>
</tbody>
</table>

SD = standard deviation.
with subsequent infusions. However, the type of skin reaction varied with subsequent administrations. **Fever**

After a median of two cycles, five patients developed febrile reactions following oxaliplatin infusion. In all of these cases, fever developed within 24 hours of infusion and infectious etiology was ruled out. Fever (above 38°C) was treated with acetaminophen. In one instance, the patient was hospitalized and treated with intravenous fluids. He defervesced within 24 hours. Oxaliplatin therapy was continued in all five patients. One of these patients experienced repeat episodes of fever with two subsequent infusions, which were treated with acetaminophen. **Respiratory Symptoms**

Five patients experienced respiratory symptoms, including wheezing, shortness of breath, and chest tightness, during oxaliplatin infusion. These were treated with diphenhydramine and dexamethasone. One patient with underlying asthma and another with fibrosis and pneumonia experienced shortness of breath during infusion. These events were not included as hypersensitivity reactions, because it was difficult to exclude the underlying disease process as a cause of these symptoms. **Ocular Symptoms**

Two patients experienced ocular symptoms; one had lacrimation following oxaliplatin infusion and the other reported blurring of vision. The patient with lacrimation experienced respiratory symptoms at the same time. This patient received a subsequent infusion of oxaliplatin over 6 hours without recurrence of symptoms. The other patient refused further chemotherapy. **Desensitization Regimen**

One patient experienced an anaphylactic reaction after his sixth infusion. He developed swelling of the tongue and face, shortness of breath, itching, chills, and slurred speech. The patient was treated with diphenhydramine, meperidine, dexamethasone, and intravenous fluids. Chemotherapy infusion was stopped. He was treated with oral dexamethasone and diphenhydramine for the next 3 days, and his symptoms resolved uneventfully. However, 2 weeks later this patient was re-treated with a regimen based on the carboplatin desensitization protocol described earlier.[19,20] Treatment with oxaliplatin was administered in the intensive care unit as four gradually escalating doses over 10.5 hours as follows:

1. 0.1% of the full dose administered over 90 minutes preceded by dexamethasone (8 mg), diphenhydramine (50 mg), and famotidine (20 mg) intravenously. These premedications were repeated prior to each of the following 3 infusions.
2. 1% of the full dose infused over 90 minutes.
3. 10% of the full dose administered over 90 minutes.
4. Remainder of the full dose (140 mg) administered over 6 hours. The patient tolerated the above regimen well and experienced no toxicity. Subsequent oxaliplatin infusions were administered in full dose (158 mg) over 6 hours, and the patient tolerated three such infusions after undergoing desensitization. Pretreatment dexamethasone, diphenhydramine, and H2 blockers were administered with each infusion. However, during the fourth infusion after desensitization-after receiving one-fifth of the due dose-the patient developed itchiness, rash, flushing, and slurring of speech. No subsequent oxaliplatin was administered to this patient. **Further Discussion**

Hypersensitivity or anaphylactic reactions are characterized by the contraction of smooth muscles and dilatation of capillaries due to the release of biologically active amines as a result of the reaction between antigens and mast cell bound antibodies (eg, immunoglobulin [Ig]E).[15] These reactions usually follow multiple doses, indicating the need for repeated exposure to antigen for eliciting the immune response. Occurrence of these reactions after initial exposure is consistent with IgE-mediated type I hypersensitivity. Idiosyncratic reactions are abnormal reactions to a drug that are not antibody-related, the onset of which may be delayed instead of immediate. Hypersensitivity reactions to platinum compounds have been well documented. Such reactions were reported in platinum refinery workers as early as 1945[16] and have been specifically described for cisplatin and carboplatin.[12-15,17] Newman Taylor et al demonstrated that HLA phenotype has an important role in sensitization to inhaled haptons of complex platinum salts, thus placing certain individuals at higher risk.[18] **Incidence of Hypersensitivity**

Most reactions noted in our study were suggestive of type I hypersensitivity. Fever and respiratory symptoms occurring hours after completion of the infusion, however, suggest an idiosyncratic effect and were also noted in our study. It is currently believed that most idiosyncratic reactions are immune-mediated and caused by immunogenic conjugates formed from the reaction of a reactive metabolite of a drug with cellular proteins.[19] Tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 are elevated during these reactions.[20] Oxaliplatin (behaving as a hapten) has been associated with immunohemolytic anemia inducing IgG antibodies bound to red cell membrane, which demonstrates its immunogenic potential.[21]
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Hypersensitivity reactions to oxaliplatin and reported 17 hypersensitivity reactions in 124 patients (13% incidence), occurring after mean infusion number 9.4 (range: 2-17).[14] The incidence of hypersensitivity reactions in our study was 18.9%. The occurrence of hypersensitivity was at median infusion number 3 in our study. The reason for early development of reactions in our study is unclear. However, individual case reports describe hypersensitivity reactions during cycles 3 through 12.[22] Treatment

These reactions were treated symptomatically with antihistamines (H1 blockers) and antipyretics. If patients developed hypersensitivity symptoms during oxaliplatin infusion, they were treated with intravenous diphenhydramine and dexamethasone, and the infusion was slowed or discontinued depending upon the severity of the reaction. If a reaction such as rash, itching, or fever appeared later or at home, patients were instructed to take oral diphenhydramine and evaluated in the outpatient clinic. These patients were premedicated with antihistamines for subsequent infusions. Pulmonary symptoms such as wheezing, shortness of breath, and chest tightness were also noted in our study. These symptoms are presumably due to bronchospasm. Uncommonly, oxaliplatin can cause acute lung injury as demonstrated by bronchoalveolar lavage. This syndrome resolved with steroid therapy.[23] Desensitization Strategies

The solitary severe anaphylactic reaction observed in our study occurred during the sixth infusion and consisted of tongue swelling, slurring of speech, chest tightness, and hypotension. As the patient had not experienced any previous allergic reactions, we can postulate that this event may have resulted from sensitization during previous infusions. This reaction may be IgE-mediated, with the platinum compound behaving as a hapten. A component of non-immune-mediated (idiosyncratic) histamine release may also have been responsible: Platinum salts can release histamine directly from mast cells and basophils.[24] Desensitization strategies have been employed when continued administration of the offending agent or allergen is deemed essential. The mechanism of desensitization is not completely understood. It is thought that when very dilute allergen is administered, it stimulates the production of IgG and IgA. These immunoglobulins then act as blocking antibodies to bind and neutralize much of the allergen before it can bind to the deeper cell-bound IgE on the mast cells in the connective tissue. The allergen also appears to suppress production of IgE by inducing tolerance and/or by activating T8-suppressor cells. We employed a strategy to "desensitize" this patient, based on a desensitization protocol employed for carboplatin hypersensitivity.[25] However the patient developed a similar reaction during the 10th infusion (4th after desensitization). Recurrence of hypersensitivity reactions after desensitization has been described with carboplatin. Rose et al, reported their experience with carboplatin desensitization in 33 patients with documented hypersensitivity.[26] Twenty-nine patients were successfully rechallenged (88%), whereas four developed recurrent symptoms precluding further administration. Three additional patients developed symptom recurrence after two, three, and six subsequent courses. Thus, 21% of patients (7/33) developed recurrence despite desensitization procedure. This may have also been the case with our patient and does not necessarily reflect failure of the desensitization protocol. Two case reports describe successful results using a similar desensitization protocol for oxaliplatin.[13,27] Interestingly, all the patients in this study were premedicated with dexamethasone and ondansetron as a component of a "standard antiemetic" regimen prior to the oxaliplatin infusion. Dexamethasone may have influenced the severity and time course of the hypersensitivity reactions observed. As a result, we may have missed minor reactions. Reducing and Predicting Hypersensitivity

Measures to decrease hypersensitivity reactions may include prolongation of infusion time to 6 hours and chronomodulation. When the infusion of oxaliplatin is prolonged to 6 hours or more, hypersensitivity reactions decrease in incidence as seen in some of our patients. Giacchetti et al reported one hypersensitivity reaction among 100 patients treated with a 6-hour oxaliplatin infusion.[28] Chronomodulation may also lead to decreased hypersensitivity. It has been shown that peak levels of histamine and other mediators occur between midnight and 4 AM, leading to exacerbation of asthma during those hours.[29] Several trials employed the concept of chronomodulation with oxaliplatin, 5-FU, and leucovorin to improve therapeutic efficacy in gastrointestinal malignancies.[30-32] Fewer hypersensitivity reactions were noted in these trials.[31,32] Intradermal skin testing may help determine hypersensitivity. Zanatti et al described a skin-testing protocol for carboplatin hypersensitivity.[33] Garufi et al studied 20 patients with advanced colorectal carcinoma and showed that an intradermal test could be used to predict hypersensitivity to oxaliplatin.[34] Conclusions

Our study supports the conclusion that hypersensitivity reactions secondary to oxaliplatin are frequent despite the routine use of dexamethasone. Given that oxaliplatin is well established in the treatment of gastrointestinal and...
gynecologic malignancies, we are likely to encounter more hypersensitivity reactions in the future. Our findings also demonstrate the benign nature of most occurrences. Fatal anaphylactic reactions are uncommon; desensitization protocols and methods to predict hypersensitivity using skin testing need further investigation.

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