Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule

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Oxaliplatin is a third-generation platinum analog that is used mainly to treat advanced colorectal cancer. The reported incidence of hypersensitivity reactions to oxaliplatin, especially after multiple cycles of therapy, is less than 1%. We report a patient with metastatic colon cancer who developed a hypersensitivity reaction to oxaliplatin during the sixth cycle of combination chemotherapy with oxaliplatin, high-dose 5-fluorouracil and leucovorin. The same reaction occurred again after re-exposure to oxaliplatin 2 weeks later even with prophylactic administration of steroids and H_1 antihistamines. After failing third-line treatment with oral tegafur-uracil, we desensitized the patient by using a fixed-rate 24-h continuous infusion of dilute oxaliplatin (0.15 mg/ml), in addition to steroids and H_1 antihistamines. He had no hypersensitivity reaction during or after that infusion or when the same concentration was infused in the same way 2 weeks later. Because his condition subsequently deteriorated and the cancer progressed, no further oxaliplatin was given. Our experience does demonstrate, however, that a fixed-rate 24-h continuous infusion of oxaliplatin in a low concentration may prevent a hypersensitivity reaction in a previously sensitized patient. *Anti-Cancer Drugs* 15:605–607 © 2004 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2004, **15**:605–607

Keywords: desensitization, hypersensitivity, oxaliplatin

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Received 23 September 2003 **Revised form accepted** 10 March 2004

Introduction

Oxaliplatin, a third-generation platinum analog, is used mainly to treat advanced colorectal cancer. When used in combination with 5-fluorouracil and leucovorin, it has shown promising activity in previously treated and untreated patients with metastatic disease [1,2]. Oxaliplatin can be easily and safely administered on an outpatient basis. However, hypersensitivity and idiosyncratic reactions have occurred. The reported incidence of hypersensitivity to oxaliplatin is less than 1%, an improvement over cisplatin and carboplatin, which are reported to cause hypersensitivity in up to 5% of cases [3,4]. We report a patient with metastatic colon cancer who had a hypersensitivity reaction to oxaliplatin which we successfully managed with desensitization.

Case report

A 73-year-old Taiwanese man had advanced colon cancer with multiple liver metastases and had failed first-line combination chemotherapy including irinotecan. He was then treated with oxaliplatin (85 mg/m^2) given as a 2-h i.v. infusion at a concentration of 0.6 mg/ml, in combination with high-dose 5-fluorouracil and leucovorin (HDFL) on a biweekly schedule. He had no history of any allergic disorder. The regimen included routine antiemetic prophylaxis with i.v. dexamethasone 10 mg and metoclopramide 9 mg, along with oral lorazepam 2 mg, 30 min prior to the administration of oxaliplatin. He tolerated the chemotherapy well for 5 cycles.

During the sixth cycle, however, the patient experienced marked abdominal distention, heat, and pruritus of the trunk and extremities 30 min after the oxaliplatin infusion was begun. There was no fever, chills, dyspnea or vomiting. The patient appeared flushed, with generalized erythema of the trunk and extremities. There was no wheezing or abdominal tenderness. The oxaliplatin infusion was stopped and he was given 30 mg of diphenhydramine i.v., followed by 50 mg orally 4 times a day. The symptoms subsided gradually over the following 2 h. The HDFL was then given without any acute adverse effects.

Because his cancer had been responding to the oxaliplatin–HDFL combination, we tried giving it again 2 weeks later. Pretreatment prophylaxis was given as before with i.v. metoclopramide and dexamethasone (5 mg this time), but with the addition of 30 mg of diphenhydramine. However, the patient again had a similar reaction 70 min after oxaliplatin was begun, although less intense than

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previously. The infusion was discontinued and he was given i.v. diphenhydramine and hydrocortisone, with gradual resolution of the symptoms. The HDFL was then continued. An episode of fever was noted on the next day which subsided after treatment with antibiotics.

Subsequently, the patient was begun on oral tegafur-uracil, but his liver metastases progressed during the 2 months he was on this agent. Since his best response had been to the oxaliplatin–HDFL combination, we elected to try desensitizing him to oxaliplatin by using a fixed-rate 24-h continuous infusion of a more dilute solution (0.15 mg/ml). The same prophylaxis as before, including diphenhydramine, was given 30 min prior to the administration of oxaliplatin and the patient was also told to take 50 mg diphenhydramine orally 4 times for 1 day. He had no hypersensitivity reaction during or after the chemotherapy. He underwent one more cycle using the same dilute, 24-h infusion of oxaliplatin 2 weeks later. He developed a leukopenic fever during the chemotherapy which was treated with antibiotics. Because his clinical condition deteriorated and his cancer progressed thereafter, the oxaliplatin was discontinued.

Discussion

Acute adverse effects of oxaliplatin include nausea, vomiting, diarrhea, myelosuppression and peripheral neuropathy. Hypersensitivity and idiosyncratic reactions have been reported, with most cases occurring after multiple cycles of therapy (range 3–25 cycles) [5]. Thomas *et al.* recently reported an incidence of hypersensitivity reactions to oxaliplatin (in the same combination regimen and infusion schedule that we used) of 0.55% [3]. According to Misset, the incidence of grade 3/4 allergic reactions to oxaliplatin is less than 1% [6]. This is much lower than the incidence of hypersensitivity reactions to carboplatin, which has ranged from 17 to 27% after more than seven courses of therapy [7,8]. On the other hand, Meyer *et al.* suggested that oxaliplatin hypersensitivity was under-diagnosed, with mild symptoms being missed. They estimated the true incidence to be approximately 12% [5]. This controversy will only be resolved by a careful search for the clinical manifestations of these hypersensitivity reactions.

Hypersensitivity and idiosyncratic reactions present differently. Hypersensitivity reactions are characterized by the development of symptoms and signs during or shortly after the completion of oxaliplatin infusion [3]. The clinical severity of hypersensitivity reactions ranges from an asymptomatic rash to severe anaphylaxis, and the symptoms may include skin rash, pruritus, flushing, a burning sensation, dizziness, facial edema, nausea, vomiting, abdominal pain, shortness of breath, bronchospasm and anxiety [5,9,10]. Idiosyncratic reactions, on the other hand, may be delayed until several hours after oxaliplatin infusion. These reactions usually present with chills, fever, abdominal pain, nausea and diarrhea, with or without hypotension [11,12]. Our patient's symptoms were most consistent with a hypersensitivity reaction, classified as grade 2 (moderate severity) [13].

The mechanism of hypersensitivity to oxaliplatin is not well understood. The characteristic clinical manifestations suggest a type I IgE-mediated reaction which initiates the release of chemical mediators resulting in vasodilation and edema. Meyer *et al.* suggested that a type I IgE-mediated reaction to oxaliplatin was comparable to reactions to cisplatin and carboplatin [5,14]. Several reports of antibody-mediated reactions to oxaliplatin, including hemolytic anemia and Evan's syndrome, also support the concept that this drug acts as an antigen [15–17].

On the other hand, Santini *et al.* and Tonini *et al.* reported that idiosyncratic reactions to oxaliplatin were associated with a massive release of cytokines such as tumor necrosis factor-α and IL-6, and that the symptoms were ameliorated by steroids, with a significant decrease in cytokine levels [11,12]. They recommended prophylactic steroids when giving oxaliplatin to prevent an idiosyncratic reaction. However, Stahl *et al.* observed that allergic reactions might still occur after steroid prophylaxis [18]. From the experience of Thomas *et al.*, we believe that the prophylactic effect of steroids depends on the dose and dosing schedule. Larger, multiple doses of steroids may be required before the administration of oxaliplatin [3].

An intradermal skin test for hypersensitivity to oxaliplatin has been reported in two small series to be 75–80% accurate [5,10]. The investigators suggested that desensitization might be considered for patients in whom oxaliplatin would be beneficial, but who had a mild to moderate skin reaction. Rechallenge probably should not be attempted, however, for those with a markedly positive skin test. Garufi *et al.* reported a patient with a negative skin test reaction who still developed severe hypersensitivity after rechallenge with oxaliplatin [10]. A negative skin test reaction thus does not preclude the possibility of an allergic reaction or even anaphylaxis to oxaliplatin. They still recommend a skin test, however, once the cumulative oxaliplatin dose is greater than 600 mg/m^2.

A desensitization protocol using a dilute oxaliplatin infusion over a prolonged period has been successfully used by Meyer *et al.* [5]. To avoid idiosyncratic reactions, Schull *et al.* proposed a 48-h continuous infusion schedule that resulted in much lower peak plasma concentrations of the platinum compound and its metabolites [19]. Patients treated with their protocol had only minor or delayed reactions, with clinically negligible release of

cytokines. We chose a 24-h continuous infusion desensitization schedule instead of 48 h, as this shortened the length of hospitalization, thus reducing cost and inconvenience. Schull *et al.* did not report the exact concentration of their infusion, so we could not compare it with our protocol. However, it is reasonable to assume that our 24-h dilute infusion also reduces the plasma concentrations of oxaliplatin and its metabolites compared with the normal 2-h infusion in the standard protocol. An additional advantage of this method is that the total dose of oxaliplatin does not need to be changed. While the exact mechanism remains to be explored, our experience suggests that the method may successfully prevent hypersensitivity reactions to oxaliplatin.

Thomas *et al.* also reported successful abortion of hypersensitivity reactions by pretreatment with steroids and H_1 and H_2 antihistamines [3]. They reported three patients who were successfully rechallenged with oxaliplatin after oral dexamethasone 20 mg, 6 and 12 h before beginning oxaliplatin, plus i.v. methylprednisolone 125 mg, diphenhydramine 50 mg and cimetidine 50 mg, all given 30 min before oxaliplatin. As yet, there are no reports of combined use of such a protocol along with a longer, dilute infusion of oxaliplatin.

The severity of a hypersensitivity reaction to oxaliplatin is unpredictable and anaphylactic reactions may occur within minutes of beginning the infusion. Several cases of severe anaphylaxis have been reported [9,20,21]. Initial management of the anaphylaxis should include stopping the infusion and standard treatment with epinephrine, corticosteroids and antihistamines. Other supportive measures such as macromolecules, supplemental oxygen and i.v. fluids can be used as needed [9]. Rechallenge with oxaliplatin after severe anaphylaxis is generally not recommended. However, Bhargava *et al.* recently reported a successful desensitization protocol in one patient [21]. After premedicating the patient 100 mg of i.v. hydrocortisone, they administered increasing concentrations of oxaliplatin in 100 ml of D5W infused over 1 h. They began with a 1:10 000 dilution, followed by 1:1000, 1:100 and then 1:10. They were then able to infuse the rest of the total oxaliplatin dose for that cycle of chemotherapy over the next 4 h. Careful monitoring of vital signs is mandatory during desensitization. The risks and benefits of rechallenge with oxaliplatin after severe anaphylaxis should be carefully judged according to the clinical situation.

Conclusion

Although no deaths attributable to oxaliplatin hypersensitivity have been reported, the potential for life-threatening reactions must always be kept in mind. Prompt recognition and treatment of a hypersensitivity reaction is of course mandatory. Based on our experience, a patient who has had a mild to moderate reaction may still benefit from oxaliplatin if it is administered in a low concentration over at least 24 h. It remains to be seen if further studies will confirm the clinical efficacy of this desensitization schedule.

Acknowledgments

We thank Dr Mary Jeanne Buttrey for editing the manuscript.

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