

Research Letter

Desensitization to Oxaliplatin with Two Stages of Premedication in a Patient with Metastatic Rectal Cancer

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ABSTRACT

Oxaliplatin is a therapeutic platinum compound used for the treatment of colorectal cancer; however, it might induce hypersensitivity reactions, a critical situation that requires discontinuation of chemotherapies that contain oxaliplatin. Independent attempts of oxaliplatin desensitization have been reported, with mostly successful results. This letter reports a 53-year-old Japanese woman (weight, 70 kg) with chemorefractory metastatic rectal cancer who had undergone surgical intervention twice and received 3 treatment regimens. The patient developed grade 3 hypersensitivities to oxaliplatin during cumulative cycles of the FOLFOX (5-fluorouracil/leucovorin/oxaliplatin)-4 regimen. After the subsequent regimen failed, she was desensitized using a protocol of an 8-hour series of diluted-oxaliplatin infusions. Because, according to previously published desensitization reports, hypersensitivity reactions might recur during the final bag infusion of oxaliplatin despite intensive premedication, prophylactic antiemesis, corticosteroids, and antihistamines were administered twice (ie, before and during the oxaliplatin infusion). Allergic reactions were successfully and efficiently prevented with the 2 stages of intensive premedication in this patient who was able to receive oxaliplatin and had stabilized lung metastases. She was able to undergo desensitization for 5 cycles until acute development of obstructive pneumonia. In this report of a previously sensitized patient, a type I hypersensitivity reaction was successfully circumvented with 2-staged premedication for oxaliplatin desensitization. The optimum desensitization protocol for oxaliplatin administration in terms of efficacy and tolerability still needs to be defined. (*Clin Ther.* 2008;30:1160–1165) © 2008 Excerpta Medica Inc.

Key words: oxaliplatin, hypersensitivity, desensitization, premedication.

INTRODUCTION

Oxaliplatin is a third-generation organoplatinum approved in Japan for use as a monotherapy or in combination with 5-fluorouracil (5-FU) for the treatment of a variety of solid tumors, including colorectal carcinoma.^{1,2} Its acute toxicities include neutropenia, thrombocytopenia, nausea, diarrhea, emesis, paresthesia, and dysesthesias.^{3,4} In addition to these adverse effects, patients may develop allergic reactions to oxaliplatin (reported incidence after multiple cycles of therapy, 2%–15% [range, 1–14 cycles; median, 7]).^{3,4}

This letter presents a case of oxaliplatin desensitization (characterized by sequential dilutions of oxaliplatin and prophylactic antiemesis, steroids, and antihistamines at 2 scheduled times) in a patient with metastatic rectal cancer.

CASE SUMMARY

A 53-year-old Japanese woman (weight, 70 kg; body surface area, 1.76 m²) with metastatic rectal cancer and who developed grade 3 hypersensitivity to oxaliplatin presented to the Odaira Memorial Tokyo Hitachi Hospital, Tokyo, Japan. She had undergone low anterior resection for rectal carcinoma at the age of 46 years (April 1999). Metastasized lung tumors were resected in December 2002. The patient received IV irinotecan and radiotherapy for metastases in peritracheal lymph nodes detected subsequently. Nonetheless, multiple refractory tumors appeared in the lungs in December 2004, and the patient received UFT (tegafur/uracil) and l-LV (levofolinate; the active isomer of the racemic leucovorin) as second-line chemotherapy. In Sep-

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tember 2005, the patient was switched to monthly 5-FU and I-LV infusion.

Because all preceding therapies failed, in May 2006 (patient age, 53 years), a FOLFOX (5-fluorouracil/leucovorin/oxaliplatin)-4 regimen was introduced (oxaliplatin 85 mg/m² [total dose, 150 mg] over 2 hours [day 1] plus LV5FU2 [biweekly leucovorin/5-fluorouracil] [ie, I-LV 100 mg/m² over 2 hours, bolus 5-FU 400 mg/m², and continuous 5-FU infusion 600 mg/m² over 22 hours (days 1–2), every 2 weeks]^{1,5}) (Figure). The patient underwent 6 cycles of FOLFOX-4 uneventfully. In cycle 7, erythema of the face and upper extremities suddenly (within ~15 minutes after the start of oxaliplatin infusion) developed, accompanied by an irritable feeling. These acute symptoms, deemed an allergic reaction, resolved within an hour with the use of hydroxyzine and famotidine. Because no delayed adverse reactions were noted, the patient received a full dose of oxaliplatin as well as the subsequent LV5FU2 course in this cycle. In the next cycle, she was premedicated with diphenhydramine 50 mg PO, dexamethasone 20 mg IV, and famotidine 20 mg IV. Nonetheless, the allergic reaction recurred, with severe symptoms developing 10 minutes after the oxaliplatin infusion was initiated; in addition to difficulty breathing, the patient experienced a burning sensation in the mouth and perineum, palpitations, and sweating. Pulse oximetry found reduced oxygenation (83% saturation on room air). The oxaliplatin infusion was discontinued immediately, and oxygen was provided via a nasal cannula. The patient's symptoms subsided within an hour.

Through the FOLFOX-4 cycles, constant regression of the disease was observed for the first time. However, because the patient's symptoms were considered potentially life-threatening, chemotherapy was switched to the FOLFIRI (5-fluorouracil/leucovorin/irinotecan) regimen in October 2006. Unfortunately, the metastases increased in size again, and new metastasized tumors appeared in the lungs. Because there were no other promising chemotherapeutic drugs or other hopeful treatment modalities as of March 2007, the patient was expected to survive ≤1 month without the reintroduction of oxaliplatin.

After written informed consent was obtained from the patient, the first desensitization was implemented in April 2007, as described below. Intradermal skin testing with oxaliplatin, performed in advance,⁶ elicited a positive reaction at dilution 10⁻¹.

The desensitization protocol is illustrated in the figure. On day 1, the patient was first premedicated with oral diphenhydramine 50 mg and domperidone 10 mg, plus a 15-minute IV infusion of famotidine 20 mg and dexamethasone 20 mg dissolved in 100 mL isotonic saline. Starting at 10 AM, she was given 1-hour infusions of 0.015, 0.135, 1.35, and 13.5 mg of oxaliplatin (1/10,000, and close to 1/1,000, 1/100, and 1/10 of the dose of 85 mg/m² [150 mg/body], respectively) diluted in 100 mL of 5% dextrose water. Hydrocortisone 100 mg and granisetron 3 mg in 50 mL of 5% dextrose water were then administered as the second premedication, and the remaining 135 mg of oxaliplatin in 500 mL of 5% dextrose water was infused over 4 hours (2–6 PM). If no severe hypersensitivity reactions were noted, the LV5FU2 regimen was to be initiated in the middle of the final oxaliplatin infusion (ie, at 4 PM). The patient's vital signs were carefully monitored throughout the entire desensitization course, which ended at 4 PM on day 2.

The patient underwent 5 additional cycles of desensitization, with no allergic events noted. The metastasized tumors had stabilized throughout the treatment cycles. As a result, the patient survived ~2 months longer than would have been expected with the use of any other treatment option; however, because of the acute development of obstructive pneumonia, the patient died in June 2007.

DISCUSSION

Patients allergic to oxaliplatin might exhibit various symptoms, such as bronchospasm, dyspnea, edema (of the eye, face, and/or hands), erythema, itching, laryngospasm, pruritus, sweating, and/or urticaria.^{3,4} These reactions typically occur 10 to 15 minutes after the start of infusion and have been ascribed to an immunoglobulin E-mediated, type I hypersensitivity. In ~1% of such patients, a potentially life-threatening allergic reaction is immediately manifest.^{3,4}

In the English literature (MEDLINE search; key terms: *oxaliplatin*, *hypersensitivity*, and *desensitization*; years searched: 1998–2007), 8 case reports of desensitization to oxaliplatin have been published (Table).^{8–15} The specific procedures in previous desensitization protocols seem to have been determined empirically; however, the majority have included the administration of increasing concentrations of oxaliplatin, starting with 1:10,000 dilution, followed by 1:1000, 1:100, and 1:10.^{9,10,12–15} The remainder

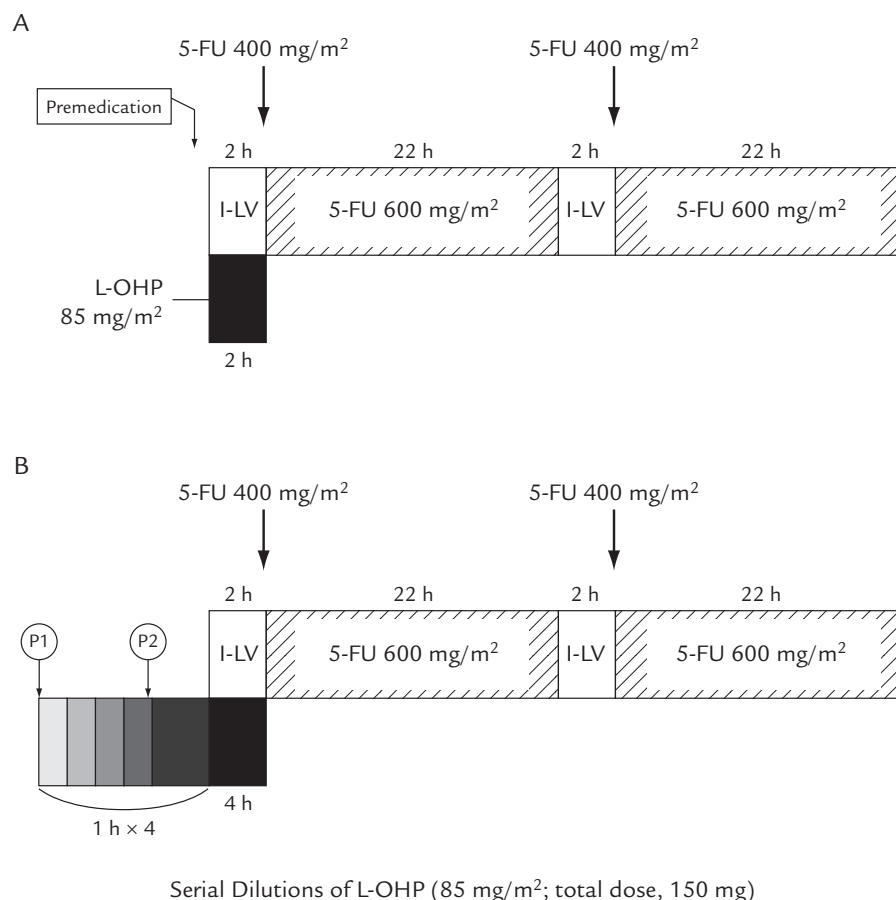


Figure. (A) Schematic time schedule of the standard FOLFOX (5-fluorouracil [5-FU]/leucovorin/oxaliplatin [L-OHP])-4 regimen in Japan. Patients are first premedicated with routine antiemetic prophylaxis (granisetron hydrochloride 3 mg) and dexamethasone 8 mg. Both oxaliplatin (L-OHP; 85 mg/m²) and leucovorin (I-LV; 100 mg/m²) are then infused over 2 hours, followed by a bolus (400 mg/m²) and 22-hour continuous (600 mg/m²) infusion of 5-FU on day 1. The infusion of I-LV and 5-FU is repeated on day 2. (B) Desensitization protocol for oxaliplatin in combination with I-LV and 5-FU infusion (the LV5FU2 regimen). After the first premedication consisting of oral diphenhydramine 50 mg, domperidone 10 mg, IV famotidine 20 mg, and dexamethasone 20 mg (P1), infusions of a series of diluted oxaliplatin (1:10,000, similar to 1:1000, 1:100, and 1:10 dilutions of the total dose) are carried out over 4 hours (1 hour for each dilution). IV hydrocortisone 100 mg and granisetron 3 mg are administered as the second premedication (P2), followed by infusion of the remaining dose of oxaliplatin over the next 4 hours. Two hours after the start of the infusion of the last dose of oxaliplatin, the LV5FU2 course is initiated.

Table. Outline of published desensitization protocols for oxaliplatin hypersensitivity.

Study	No. of Patients	Premedication	Dilution, Dose and/or Concentration Given, No. of Steps	Infusion Time
Schüll et al ⁸	1	Ondansetron 8 mg IV, high-dose dexamethasone IV, and antihistamine IV	Fixed-rate, continuous	48 Hours
Meyer et al ⁹	1	NS (adapted from Goldberg et al ⁷ protocol)	From 1:1000 through 1:1, 4 steps	NS
Gammon et al ¹⁰	1	Dexamethasone IV, diphenhydramine IV, and hydrocortisone 100 mg IV	From 1:10,000 through 1:1, 5 steps (total dose, 173 mg)	1 Hour × 4 steps, 4 hours for last step (total, 8 hours)
Lim et al ¹¹	1	Diphenhydramine 50 mg PO QID, metoclopramide 9 mg IV QD, and diphenhydramine 30 mg IV QD	Fixed-rate, continuous 0.15 mg/mL	24 Hours
Mis et al ¹²	1	Prednisolone 20 mg PO QID, magnesium sulfate 1 g IV, calcium gluconate 1 g IV, ondansetron 8 mg IV, dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and cimetidine 300 mg IV	From 1:10,000 through 1:1 (0.014–124 mg), 5 steps (total dose, 140 mg)	1 Hour × 4 steps; 4 hours for the last step (total, 8 hours)
Herrero et al ¹³	5	None	From 0.003 mg/min through 0.75 mg/min (0.01–0.18 mg/mL), several steps	30–60 Minutes × several steps (NS) (total, 5–6 hours)
Edmondson et al ¹⁴	1	None	From 1:10,000 through 1:2 (0.014–80 mg), 12 steps	5 Minutes × 5 steps, 15 minutes × 4 steps, 30 minutes × 2 steps, 60 minutes for last step (total, 205 minutes)
Wrzesinski et al ¹⁵	1	Ondansetron 8 mg IV BID, magnesium sulfate 1 g IV BID, calcium gluconate 1 g IV BID, famotidine 20 mg IV QD, dexamethasone 20 mg IV QD, and diphenhydramine 50 mg IV QD	From 1:10,000 through 1:1, 5 steps	1 Hour × 4 steps, 2 hours for the last step (total, 6 hours)
Current	1	Famotidine 20 mg IV QD, dexamethasone 20 mg IV QD, diphenhydramine 50 mg PO QID, domperidone 10 mg PO QID, hydrocortisone 100 mg IV QD, and granisetron 3 mg IV QD	From 1:10,000 to 1:1 (0.015–13.5 mg), 5 steps (total dose, 150 mg)	1 Hour × 4 steps, 4 hours for the last step (total, 8 hours)

(~90% of total dose) of oxaliplatin is infused over a longer duration.^{10,14,15} Of note, a US group reported that in a 50-year-old sensitized patient with metastatic colon cancer, a macular rash developed over the lower extremities during a 2-hour infusion of the final dose of oxaliplatin in the initial desensitization.¹⁰ By modifying the last step to a 4-hour infusion, the subsequent desensitization became tolerable in this patient.¹⁰ Distinct from the sequential dilution, other groups have used desensitization protocols composed of a fixed-rate infusion of oxaliplatin.^{8,11} However, protracted infusion might reduce the plasma concentration of oxaliplatin,^{8,11} resulting in decreased antitumor activity. In a randomized clinical trial in ~185 patients with previously untreated metastases from colorectal cancer, the efficacy and tolerability of a chronomodulated (10 AM–10 PM) infusion of oxaliplatin for 5 consecutive days were compared with those of fixed-rate 24-hour infusion. Chronotherapy in the daytime was associated with a higher response rate (51% vs 29%; $P = 0.003$), longer time to progression (6.4 vs 4.9 months; $P = 0.006$), and decreases in the rates of some adverse events (eg, mucositis [14% vs 76%; $P < 0.001$]).¹⁶

Taking all of these results into consideration, we employed serial dilutions of oxaliplatin for desensitization. The desensitization protocol was designed to comprise a daytime 4-hour infusion of the last 90% of total dose in 500 mL of 5% dextrose water. Furthermore, a characteristic of the treatment used in the present study was an additional premedication scheduled just prior to the final bag infusion of oxaliplatin to prevent a late allergic reaction. In this regard, Wrzesinski et al¹⁵ described the second administration of magnesium and calcium salts during desensitization, with a similar intention. In contrast, 2 other protocols did not include any premedication,^{13,14} one of which aimed to easily detect early signs of anaphylaxis,¹³ in contrast to our stance that we should strive to minimize patients' risk for hypersensitivity reactions.

CONCLUSIONS

In this report of a previously sensitized patient, a type I hypersensitivity reaction was successfully circumvented with this 2-staged premedication for oxaliplatin desensitization. The optimum desensitization protocol for oxaliplatin administration in terms of efficacy and tolerability still needs to be defined.

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REFERENCES

- de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18:2938–2947.
- André T, Boni C, Mounedji-Boudiaf L, et al, for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343–2351.
- Maindrault-Goebel F, André T, Tournigand C, et al. Allergic-type reactions to oxaliplatin: Retrospective analysis of 42 patients. *Eur J Cancer*. 2005;41:2262–2267.
- Hewitt MR, Sun W. Oxaliplatin-associated hypersensitivity reactions: Clinical presentation and management. *Clin Colorectal Cancer*. 2006;6:114–117.
- André T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol*. 1999;17:3560–3568.
- Leguy-Seguin V, Jolimoy G, Coudert B, et al. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin Immunol*. 2007;119:726–730.
- Goldberg A, Confino-Cohen R, Fishman A, et al. A modified, prolonged desensitization protocol in carboplatin allergy. *J Allergy Clin Immunol*. 1996;98:841–843.
- Schüll B, Kornek GV, Scheithauer W. Idiosyncratic reaction after oxaliplatin: Circumvention by use of a continuous infusional administration schedule. *Ann Oncol*. 2001;12:1653–1654.
- Meyer L, Zuberbier T, Worm M, et al. Hypersensitivity reactions to oxaliplatin: Cross-reactivity to carboplatin and the introduction of a desensitization schedule. *J Clin Oncol*. 2002;20:1146–1147.
- Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist*. 2004;9:546–549.
- Lim KH, Huang MJ, Lin HC, et al. Hypersensitivity reactions to oxaliplatin: A case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs*. 2004;15:605–607.
- Mis L, Fernando NH, Hurwitz HI, Morse MA. Successful desensitization to oxaliplatin. *Ann Pharmacother*. 2005;39:966–969.

13. Herrero T, Tornero P, Infante S, et al. Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. *J Investig Allergol Clin Immunol*. 2006;16:327–330.
14. Edmondson DA, Gruling BJ, Urmanski AM, et al. Oxaliplatin hypersensitivity: Case report and successful repeat desensitization. *Am J Ther*. 2007;14:116–118.
15. Wrzesinski SH, McGurk ML, Donovan CT, et al. Successful desensitization to oxaliplatin with incorporation of calcium gluconate and magnesium sulfate. *Anticancer Drugs*. 2007;18:721–724.
16. Lévi F, Zidani R, Misset JL, for the International Organization for Cancer Chronotherapy. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. *Lancet*. 1997;350:681–686.

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