

Hypersensitivity Reactions to Oxaliplatin: Identifying the Risk Factors and Judging the Efficacy of a Desensitization Protocol

Tetsuya Okayama, MD, PhD^{1,2}; Takeshi Ishikawa, MD, PhD^{1,2}; Kazuko Sugatani³; Naohisa Yoshida^{1,3}; Satoshi Kokura, MD, PhD^{1,2}; Kiyomi Matsuda³; Shigeru Tsukamoto³; Norihiko Ihara³; Yoshiaki Kuriu, MD, PhD⁴; Masayoshi Nakanishi, MD, PhD⁴; Terukazu Nakamura, MD, PhD^{3,5}; Kazuhiro Kamada, MD, PhD¹; Kazuhiro Katada, MD, PhD¹; Kazuhiko Uchiyama, MD, PhD¹; Tomohisa Takagi, MD, PhD¹; Osamu Handa, MD, PhD¹; Hideyuki Konishi, MD, PhD¹; Nobuaki Yagi, MD, PhD¹; Yuji Naito, MD, PhD¹; Eigo Otsuji, MD, PhD⁴; Hajime Hosoi, MD, PhD^{3,6}; Tsuneharu Miki, MD, PhD^{3,5}; and Yoshito Itoh, MD, PhD¹

¹Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; ²Department of Cancer ImmunoCell Regulation, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; ³Medical Oncology, Kyoto Prefectural University Hospital, Kyoto, Japan; ⁴Department of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan; ⁵Department of Urology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; and ⁶Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

ABSTRACT

Purpose: We examined the clinical data of patients treated with oxaliplatin to determine the risk factors of oxaliplatin-related hypersensitivity reaction (HSR). In addition, we evaluated the efficacy of rechallenging patients with HSRs with oxaliplatin using prophylactic agents or desensitization procedures.

Methods: This study consisted of 162 patients with colorectal cancer (88 men and 74 women) who were treated consecutively at the outpatient chemotherapy department at University Hospital, Kyoto Prefectural University of Medicine. Patients underwent chemotherapy, including oxaliplatin, between March 2006 and June 2012. We analyzed the patients' clinical backgrounds (eg, age, sex, performance status, disease stage, and allergic history) to uncover any connections to the development of HSR to oxaliplatin. In addition, we rechallenged 10 patients who had oxaliplatin-related HSR using prophylactic agents or desensitization procedures.

Findings: Of 162 patients, 28 (17.2%) developed oxaliplatin-related HSRs (16, 2, 9 and 1 patient had grade 1, 2, 3, and 4 HSRs, respectively). The total cumulative dose of oxaliplatin at the onset of the HSR was 301 to 1126 mg/m² (median, 582 mg/m²), and

the first reactions developed in these patients after 5 to 17 infusions of oxaliplatin (median, 8 infusions). Logistic regression analysis indicated that sex (male: odds ratio = 3.624; 95% CI, 1.181–11.122; *P* = 0.024) and eosinophil count in peripheral blood (odds ratio = 35.118; 95% CI, 1.058–1166.007; *P* = 0.046) were independent variables for oxaliplatin-related HSRs. Rechallenging patients with prophylactic agents was successful in 2 (28.6%) of 7 patients who successfully completed their treatment. On the other hand, all 3 patients rechallenged with oxaliplatin using a desensitization protocol successfully completed their treatment without new HSRs.

Implications: In this retrospective study, we observed that being male and having higher counts of peripheral eosinophil could be predictors for HSR to oxaliplatin. In addition, this study confirms that oxaliplatin desensitization protocol allows patients who developed HSRs to continue with their treatment. However, the optimum desensitization protocol for

Accepted for publication March 9, 2015.

<http://dx.doi.org/10.1016/j.clinthera.2015.03.012>

0149-2918/\$ - see front matter

© 2015 Elsevier HS Journals, Inc. All rights reserved.

oxaliplatin administration in terms of tolerability and efficacy needs to be defined. (*Clin Ther.* 2015;■:■■■-■■■) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: colorectal cancer, desensitization, hypersensitivity reaction, oxaliplatin.

INTRODUCTION

Oxaliplatin is a third-generation platinum compound that has efficacy against colorectal cancer (CRC).¹ In Japan, oxaliplatin is approved for disease management in both metastatic and adjuvant settings in combination with 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine.^{2,3} In addition, it is also used in a wide variety of tumors, including pancreatic, biliary, gastroesophageal, and gynecologic malignant tumors.⁴ In recent years, however, the extensive use of oxaliplatin has been accompanied by an increase in various adverse reactions in patients.

The major adverse events associated with oxaliplatin include nausea, vomiting, myelosuppression, and neurotoxicity. Of these, neurotoxicity is the most prominent and limits the clinical use of oxaliplatin. In addition to cumulative neuropathy, hypersensitivity reaction (HSR) also limits the clinical use of oxaliplatin.⁴⁻⁷

Patients experiencing hypersensitivity have several symptoms, such as rash, itching, urticaria, flushing, burning, palmar, edema of the face and hands, abdominal cramping, diarrhea, back pain, and pruritus.^{5,6,8,9} In some cases, more severe symptoms manifest, such as tachycardia, bronchospasm, hypotension or hypertension, and seizures; these anaphylaxis symptoms are sometimes life-threatening. Although in earlier studies the incidence of HSR was found to be <2%, recent reports have found occurrence rates as high as 10% to 25%.^{5,7,10} Identifying high-risk patients early to expedite their treatment is of great clinical importance because oxaliplatin-related HSR may be fatal to patients in critical condition. Although oxaliplatin-related HSR is a pressing concern, little information is available on the risk factors involved, and only 4 known studies have explored this issue by multivariate analysis.¹¹⁻¹⁴ As a result, there are no confirmed risk factors for oxaliplatin-related HSR that can be effectively applied in clinical practice.

Efforts to combat oxaliplatin-related neurotoxicity have yielded progress. One such result is the stop-and-go method developed in the Optimized Leucovorin-Fluorouracil-Oxaliplatin (OPTIMOX1) trial.¹⁵ The

strategy involves treating patients intermittently by discontinuing and reintroducing oxaliplatin treatment for a defined period to avoid oxaliplatin neurotoxicity.¹⁶

The stop-and-go strategy has yielded clinical efficacy comparable to conventional continuous treatment but with lower incidences of neurotoxicity.¹⁴ However, in the OPTIMOX1 trial, the true impact of oxaliplatin reintroduction on overall survival was potentially masked by the fact that a large number of patients did not receive the planned oxaliplatin reintroduction. In further research performed on this issue, de Gramont et al¹⁷ found that oxaliplatin reintroduction had an independent and significant positive impact on overall survival (hazard ratio = 0.51, $P = 0.009$, 95% CI = 0.30-0.90) in patients with advanced CRC. Thus, in patients who develop HSR during consecutive oxaliplatin-based treatments, the expectation is that if the readministration of oxaliplatin is tolerable after a pause in treatment, it would likely have a significant positive effect on the prognosis of patients with advanced CRC.

Readministering oxaliplatin to patients with HSRs has been attempted using several methods, such as using prophylactic agents (ie, hydrocortisone and antihistamines), extending administration time, and using desensitization procedures.¹⁸⁻²⁰ Some studies have successfully readministered oxaliplatin to patients with HSRs using prophylactic agents, whereas several other studies had reported success using the desensitization protocol.²¹⁻²⁴ In many cases, treatment started with minute amounts of oxaliplatin, and then consecutively higher concentrations were administered to patients. Despite such promising outcomes, the preventive effect of premedicating and desensitizing patients with HSRs remains controversial.^{7,19,20,25}

In this study, we retrospectively analyzed the data of CRC patients treated with oxaliplatin-based chemotherapy and investigated which clinical parameters were possible risk factors for oxaliplatin-related HSR. Moreover, we evaluated the efficacy of rechallenging patients with HSRs with oxaliplatin using prophylactic agents and a desensitization protocol.

MATERIALS AND METHODS

Patients

This retrospective study is based on recorded CRC cases at the University Hospital of Kyoto Prefectural University of Medicine. The sample consisted of 162 outpatients (88 men and 74 women) with CRC, who

were treated with oxaliplatin-based chemotherapy between March 2006 and June 2012. Patients were selected consecutively with no particular exclusion criteria. All resulting oxaliplatin-related HSRs were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. This research was approved by the Ethics Commission of the Kyoto Prefectural University of Medicine. The Ethics Commission did not require written informed consent from each patient for the retrospective analysis of this research.

Desensitization Protocol

We used the modified desensitization protocol designed by Nozawa et al.²⁵ Briefly, 20 mg of dexamethasone, 20 mg of famotidine, 50 mg of diphenhydramine, and 10 mg of domperidone were administered to patients before chemotherapy. Next, starting with the weakest, a series of diluted oxaliplatin (1/10,000, 1/1,000, 1/100, and 1/10 dilutions of the total

oxaliplatin dose) was infused consecutively for 4 hours (1 hour per dilution). The fifth and final infusion of oxaliplatin was given in the next 4 hours. At the same time the last oxaliplatin infusion was started, 100 mg of hydrocortisone and 3 mg of granisetron were administered as additional premedication. Undiluted oxaliplatin was also administered for 4 hours, and for the final 2 hours, LV was infused simultaneously. Next, 5-FU (400 mg/m²) was administered by bolus injection, then immediately following, 5-FU (2400 mg/m²) was administered by continuous injection for 46 hours (Figure). If the first round of infusion was well tolerated, we skipped the 1/10,000 oxaliplatin infusion in the second round; the other infusions remained similar to that of the first round of the desensitization procedure.

Statistical Analysis

Information concerning all patients was obtained from their medical records in accordance with local

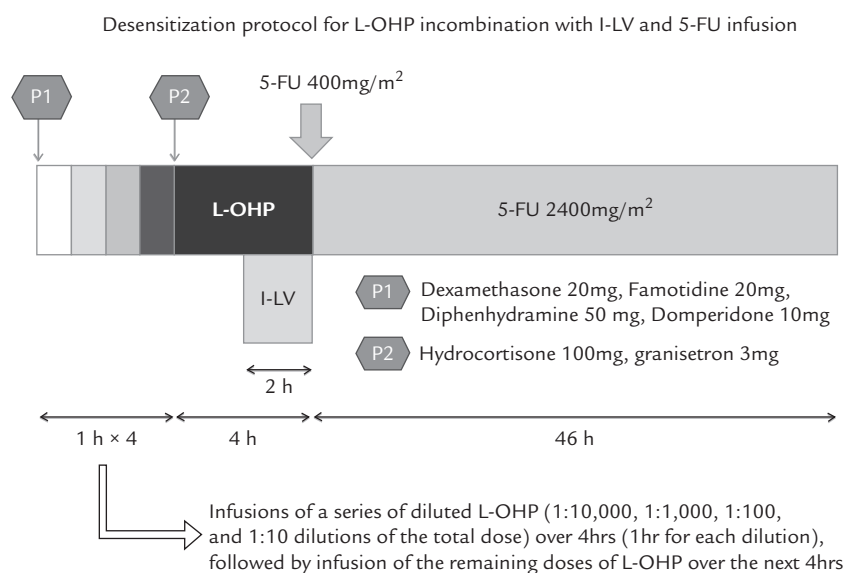


Figure. Desensitization protocol for the 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX) regimen in this study. Patients were orally premedicated with 20 mg of dexamethasone, 20 mg of famotidine, 50 mg of diphenhydramine, and 10 mg of domperidone (P1). Then a series of diluted oxaliplatin (1/10,000, 1/1,000, 1/100, and 1/10 dilutions of the total oxaliplatin dose) was infused during 4 hours (1 hour for each dilution). During this time, patients were given a second round of premedication that consisted of 100 mg hydrocortisone and 3 mg of granisetron (P2). The remaining dose of oxaliplatin was administered during the next 4 hours. For the final 2 hours of starting the remaining oxaliplatin infusion, LV was simultaneously infused. Then 5-FU (400 mg/m²) was administered by bolus injection, followed by a continuous infusion of 5-FU (2400 mg/m²) for 46 hours.

regulations. The baseline characteristics of patients were compared using the χ^2 test (applying Yates correction when necessary) for categorical variables and the t test for continuous variables. Relevant predictors of hypersensitive reactions to oxaliplatin were first examined with univariate analysis and then estimated by logistic regression analysis using a multivariate model, including all variables with a possible association with the outcomes of interest ($P < 0.20$ after univariate analysis). $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

In this study, we retrospectively analyzed the records of 162 CRC outpatients who were consecutively treated with oxaliplatin-based regimens. Their background characteristics are listed in [Table I](#). The median age was 64 years (range, 33–85 years), and of the 162 patients, 88 (54.3%) were male and 74 (45.7%) were female. Approximately 83% of patients had an Eastern Cooperative Oncology Group performance score of ≤ 1 . Ninety-seven patients (59.9%) had received modified 5-FU, LV, and oxaliplatin (mFOLFOX6; oxaliplatin (85 mg/m²) and LV (200 mg/m²) were infused for 2 hours. Subsequently, a bolus dose of 5-FU (400 mg/m²) was injected intravenously, followed by infusion of 5-FU (2400 mg/m²) for 46 hours. This regimen was repeated every 2 weeks, 48 patients received capecitabine plus oxaliplatin (XELOX; capecitabine of

1,000 mg/m² (orally administered twice a day on days 1–14) and oxaliplatin at 130 mg/m² (on day 1, as intravenous for 2 hours). The regimens were repeated every 3 weeks after initiation of the first cycle, and 17 patients received other regimens. A total of 121 patients (74.7%) were treated with oxaliplatin for palliative therapy, and 41 (25.3%) received adjuvant therapy. Ninety-seven patients (59.9%) had received oxaliplatin as first-line chemotherapy. Oxaliplatin was administered in combination with anti-vascular endothelial growth factor antibody agent in 64 patients (39.5%) and with anti-epidermal growth factor receptor antibody agents in 6 patients (3.7%).

Background of Patients Who Did or Did Not Develop HSRs

Of 162 patients, 28 (17.2%) developed oxaliplatin-related HSRs, 9 (5.6%) of whom were severe. The first reactions were evident after a median of 8 infusions of oxaliplatin (range, 5–17 infusions). The median accumulative dose was 582 mg/m² (range, 301–1126 mg/m²).

To identify the potential risk factors for the development of oxaliplatin-related HSRs, clinical variables were compared between patients who developed HSRs and those who did not. As indicated in [Table II](#), compared with patients without HSRs, the proportion of males was significantly larger and the cell counts of eosinophil and basophil in peripheral blood were significantly higher in patients with HSRs. In addition, patients with HSRs had significantly higher levels

Table I. Patient characteristics.

Characteristic	No. of Patients*
Age, median (range), y	64 (33–85)
Male/female sex	88/74
Performance status 0/1/ ≥ 2	35/99/28
Chemotherapy	
mFOLFOX6/XELOX/other	97/48/17
First-line/second-line/third-line or greater therapy	97/32/33
Metastatic/adjuvant	121/41
Nonantibody/anti-VEGF/anti-EGFR combination therapy	92/64/6

EGFR = epidermal growth factor; mFOLFOX6 = modified 5-FU, LV, and oxaliplatin; VEGF = vascular endothelial growth factor; XELOX = capecitabine plus oxaliplatin.

*Data are presented as number of patients unless otherwise indicated.

Table II. Background of patients who did or did not develop HSR.

Parameter	Patients with HSRs (n = 28)	Patients Without HSRs	P
Age, mean (SD), y	60.96 (12.02)	64.36 (10.38)	0.13
Male/female sex, no. (%)	20 (71)/8 (29)	68 (51)/66 (49)	0.046
Performance status 0/1/≥ 2, no. (%)	23 (82)/5 (18)	111 (83)/23 (17)	0.93
Allergic history, no. (% yes)	9 (32)	42 (31)	0.93
Stage I/II/IIIa/IIIb/IV no. (%)	0/0/1 (4)/1 (4)/26 (92)	1 (0.7)/1 (0.7)/6 (4.5)/9 (6.7)/116 (86.6)	0.92
Metastasis, no. (% yes)	27 (96)	120 (90)	0.254
mFOLFOX6/XELOX/other regimen no. (%)	19 (68)/8 (29)/1 (4)	78 (58)/40 (30)/16 (12)	0.38
Line of chemotherapy, mean (SD)	1.79 (1.17)	1.80 (1.35)	0.96
Nonantibody/anti-VEGF/anti-EGFR combination therapy no. (%)	12 (43)/16 (57)/0	80 (60)/48 (37)/6 (4)	0.079
Biochemical examination of blood, mean (SD)			
WBC count, $\times 10^3/\mu\text{L}$	4.82 (1.27)	4.97 (1.86)	0.69
Lymphocytes	1.57 (0.55)	1.60 (0.57)	0.81
Neutrophils	2.56 (1.03)	3.13 (4.59)	0.51
Eosinophils	0.18 (0.17)	0.13 (0.98)	0.03
Basophils	0.061 (0.185)	0.026 (0.023)	0.03
Hemoglobin, g/dL	12.81 (1.60)	11.93 (1.70)	0.01
Platelets, $\times 10^3/\mu\text{L}$	160.68 (48.01)	165.70 (78.86)	0.75
LDH, U/L	253.68 (165.01)	264.65 (150.99)	0.73
AST, U/L	34.57 (16.81)	34.28 (19.88)	0.94
ALT, U/L	35.39 (44.49)	26.10 (17.35)	0.07
ALP, U/L	419.79 (392.81)	352.37 (230.71)	0.22
γ -GT, U/L	124.96 (248.57)	70.85 (80.07)	0.04
Albumin, g/dL	3.93 (0.34)	3.94 (0.48)	0.88
Creatinine, mg/dL	0.71 (0.19)	0.69 (0.25)	0.77
HSR grades 1/2/3/4	15/4/8/1		
Total no. of therapy cycles (range)	8.5 (3–11)		
Cumulative amount of oxaliplatin (range), mg/m^2	959 (516–1500)		

ALT = alanine transaminase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; EGFR = epidermal growth factor; γ -GT = γ glutamyl transpeptidase; HSR = hypersensitivity reaction; LDH = lactate dehydrogenase; mFOLFOX6 = modified 5-FU, LV, and oxaliplatin; VEGF = vascular endothelial growth factor; WBC = white blood cell; XELOX = capecitabine plus oxaliplatin.

of hemoglobin and γ -glutamyl transpeptidase than patients without HSRs. Although the alanine transaminase level tended to be higher in patients with HSRs, the difference did not reach statistical significance ($P = 0.07$). In addition, patients with HSRs trended to be younger than those without HSRs, but this finding also did not reach statistical significance ($P = 0.13$). Other clinical factors were relatively similar between the HSR and non-HSR groups.

Next, we analyzed the potential risk factors between patients with mild HSRs (grade ≥ 2) and patients with severe HSR (grade ≤ 3). As indicated in Table III, the time between the start of oxaliplatin

infusion and the onset of HSR was significantly shorter in patients with severe HSRs than in patients with mild HSRs (18 vs 54 minutes, $P = 0.001$).

Determining Risk Factors of Oxaliplatin-Related HSR Using Multivariate Models

Logistic regression analysis using patient variables (ie, age, sex, eosinophil and basophil count in peripheral blood, hemoglobin level, alanine transaminase and γ -glutamyl transpeptidase levels, and combination with molecular target drugs, such as antivascular endothelial growth factor and anti-epidermal growth factor receptor antibodies) indicated that sex (male: odds ratio = 3.624;

Table III. Background comparison with multivariate analysis between mild and severe HSR.

Variable	Grade ≤ 2 HSR (n = 19)	Grade ≥ 3 HSR (n = 9)	P
Age, mean (SD)	58.05 (10.87)	67.11 (12.60)	0.61
Male/female sex, no. (%)	14 (73.7)/5 (26.3)	6 (66.7)/3 (33.3)	0.70
Performance status 0, 1/ ≥ 2 , no. (%)	14 (73.7)/5 (26.3)	9/0	0.09
Allergic history, no. (% yes)	6 (31.6)	3 (33.3)	0.93
mFOLFOX6/XELOX/other regimen, no. (%)	14 (73.7)/5 (26.3)/0	5 (55.6)/3 (33.3)/1 (11.1)	0.29
Line of chemotherapy, mean (SD)	1.79 (1.23)	1.78 (1.09)	0.98
Total injected oxaliplatin quantity, mean (SD), mg/m ²	609 (241)	618 (217)	0.92
Onset time from state of oxaliplatin infusion, mean (SD), min	54.26 (27.58)	17.89 (6.72)	0.001

HSR = hypersensitivity reaction; mFOLFOX6 = modified 5-FU, LV, and oxaliplatin; XELOX = capecitabine plus oxaliplatin.

95% CI, 1.181–11.122; $P = 0.024$) and eosinophil count in peripheral blood (odds ratio = 35.118; 95% CI, 1.058–1166.007; $P = 0.046$) were independent variables for oxaliplatin-related HSR (Table IV).

Oxaliplatin Rechallenge with Prophylactic Agent

Of the 28 patients who developed oxaliplatin-related HSRs, 7 were rechallenged after being premedicated with corticosteroids or administered antihistamine (H_1 and/or H_2) or both. Of these, 6 had grade 1 HSR and 1 patient had grade 3 HSR.

Two (28.6%) of 7 patients successfully completed their oxaliplatin-based treatments after being rechallenged with prophylactic agents. Three patients (42.9%) developed HSR when rechallenged. The remaining 2 (28.6%) reacted favorably to their first reintroduction to oxaliplatin but later developed HSRs after the second treatment. Treatment with oxaliplatin was discontinued in these 2 cases; however, 1 case became successful when the patient received oxaliplatin readministered with a desensitization protocol (patient 6 in Table V and case 1 discussed below).

Table IV. Logistic regression analysis using patient variables.

Parameter	OR (95% CI)	P
Age	0.984 (0.942–1.028)	0.477
Male sex	3.624 (1.181–11.122)	0.024
Biochemical examination of blood		
Eosinophil count	35.188 (1.058–1166.007)	0.046
Basophil count	240.639 (0.112–515,218.632)	0.161
Hemoglobin	1.148 (0.842–1.566)	0.383
ALT	1.008 (0.992–1.024)	0.331
γ -GT	0.999 (0.992–1.006)	0.871
Nonantibody/anti-VEGF/anti-EGFR combination therapy		0.101

ALT = alanine transaminase; EGFR = epidermal growth factor; γ -GT = γ glutamyl transpeptidase; OR = odds ratio; VEGF = vascular endothelial growth factor.

Table V. Oxaliplatin rechallenge with a prophylactic agent.

Patient No.	Age, y	Sex	Grade of Allergy	Increased Corticosteroid Dosage	Antihistamines	Desensitization	Successful Reintroduction of Oxaliplatin
1	76	M	1	Done	H ₁ , H ₂	—	o(+8 cycles)→X
2	55	M	1	—	H ₁ , H ₂	—	O
3	70	F	1	—	H ₁	—	X
4	62	M	1	—	H ₁	—	O
5	36	M	1	—	H ₁	—	X
6	74	M	3	Done	H ₁ , H ₂	Done	Premedication × desensitization o
7	72	M	1	Done	H ₁	—	o(+17 cycles)→X

H₁ = histamine 1; H₂ = histamine 2; O = success; X = unsuccess.

Meanwhile, an additional 2 of 28 HSR patients did not receive higher doses of premedication; however, they were rechallenged with oxaliplatin using a desensitization protocol (case 2 and 3 mentioned below) (Table V).

Oxaliplatin Rechallenge with Desensitization Protocol

Three of 28 HSR patients (1 with grade 2 HSR and 2 with grade 3 HSR) were rechallenged with oxaliplatin using a desensitization protocol. Their treatment and outcome are as follows.

Case 1

A 74-year-old man was diagnosed as having stage IV rectal cancer with multiple liver metastases in November 2009. From December 2009, he was treated with mFOLFOX6 chemotherapy regimen plus bevacizumab every 2 weeks as first-line therapy. The patient had a partial response with a decrease in the size of measurable liver lesions. With cycle 5 of therapy, he developed a grade 3 oxaliplatin-related HSR, exhibiting symptoms that included hypotension, rash, and abdominal pain. Two weeks later, he was rechallenged with oxaliplatin after being premedicated with 100 mg of hydrocortisone and H₁/H₂ antihistamines. Once again, the patient developed a grade 3 HSR, and treatment was discontinued. Subsequently, he was treated with 41 cycles of 5-FU, LV, and irinotecan (FOLFIRI) as second-line chemotherapy from March 2010 to November 2011, followed by 4 cycles of S-1 and irinotecan from December 2011 to

March 2012. These regimens were discontinued due to tumor progression and adverse effects. Next, he was treated with 5-FU and LV (LV5FU2) from April 2012, but after 6 cycles, this regimen was discontinued because of tumor progression.

Because there were no other alternative oxaliplatin-free chemotherapy schemes, it was suggested that the patient consider being rechallenged with oxaliplatin. After signing an informed consent, the patient was admitted to our hospital. On July 18, 2012, oxaliplatin was readministered in 5 serial dilutions from 1:10000 to 1:1 using a desensitization protocol (Figure 1). The patient tolerated this desensitization regimen very well without any symptoms of HSR. In the next cycle, he was administered oxaliplatin in 4 serial dilutions starting at 1:1000 of total dose. He subsequently tolerated an additional 7 cycles of the oxaliplatin-based regimen until January 2013 as an outpatient. Therapy was later discontinued, however, because of tumor progression and an overall deterioration in the patient's general health.

Case 2

A 55-year-old woman was diagnosed as having stage IV rectal cancer with multiple liver and lung metastases in June 2009. She had bowel obstruction and underwent palliative resection of the tumor. Approximately 3 weeks after surgery, she was treated with XELOX plus bevacizumab as first-line chemotherapy. With cycle 3 of therapy, she developed a grade 2 oxaliplatin-related HSR (dyspnea), and the

XELOX regimen was discontinued. Subsequently, she was treated with FOLFIRI plus cetuximab as second-line chemotherapy. After 3 cycles of FOLFIRI, she had tumor progression and a loss of appetite; as a result, the FOLFIRI regimen was discontinued. Because she had a partial response while taking oxaliplatin, it was thought that an oxaliplatin-based regimen was the best option to control tumor growth. The patient consented to rechallenging oxaliplatin and was admitted to our hospital on December 12, 2011. She was treated with an oxaliplatin-containing regimen using a desensitization protocol (Figure); however, although she subsequently tolerated an additional 5 cycles without HSRs, therapy was discontinued because of tumor progression.

Case 3

A 57-year-old man was diagnosed as having stage IV rectal cancer with multiple liver metastases in January 2011 and underwent palliative resection due to bowel obstruction on February 2, 2011. He was treated with mFOLFOX6 plus bevacizumab as first-line chemotherapy from March 31. With 10 cycles of chemotherapy, he developed a grade 3 HSR to oxaliplatin (dyspnea and hypotension), and the mFOLFOX regimen was discontinued. Subsequently, he was treated with 6 cycles of FOLFIRI plus cetuximab as second-line chemotherapy, but the patient experienced tumor progression. We concluded that it would be difficult to control tumor growth, and it was suggested that he be rechallenged with oxaliplatin. He consented to the treatment, and he received oxaliplatin-based treatment on January 19, 2012, using a desensitization protocol (Figure 1). Although he tolerated an additional 3 cycles without HSR, the therapy was discontinued because of central venous port infection.

DISCUSSION

Oxaliplatin, a third-generation platinum agent, is widely used in chemotherapy regimens to treat many kinds of cancers.^{1,3} It is one of the primary drugs indicated for advanced colon cancer therapy; however, patient hypersensitivity to this drug often leads to the interruption of treatment. The Multicenter International Study of Oxaliplatin/ 5FU-LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, in which >1100 patients with CRC received 5-FU with oxaliplatin, reported a 10.3% incidence of

HSR, and this was one of the major reasons the treatment was discontinued.²⁶ It was reported that the rate of occurrence of HSR was different for each generation of platinum agents,^{5,8,9,12,27} and the frequency of oxaliplatin-related HSR is relatively low. However, recently, the incidence of oxaliplatin-related HSR is increasing as a consequence of the increasing clinical use of oxaliplatin in both adjuvant and metastatic treatments of CRC and other malignant tumors.^{5,28,29} Recent reports place the incidence of HSR at 10% to 25% (1%–7.3% for events of grade ≥ 3).^{10,11,29} In this study, the incidence of oxaliplatin-related HSRs was 17.3%, whereas the incidence of severe HSR (grade 3 or 4) was comparatively low at 0.56%.

Recently, Kidera et al¹⁹ found that increased dosage of dexamethasone and antihistamine from the sixth cycle of mFOLFOX6 treatment significantly reduced the frequency of oxaliplatin-related HSR. This strategy would be promising to suppress the occurrence of oxaliplatin-related HSR, but there are drawbacks to increasing the dose of prophylactic agents, such as corticosteroids, to all patients because of the possibility of severe adverse effects. A more desirable strategy therefore would be to increase the dosage of prophylactic agents only to patients with a high risk of oxaliplatin-related HSR. However, implementing this strategy is challenging because reliable methods for predicting the risk of oxaliplatin-related HSR have not been established. Prediction methods that hold promise, such as the prick and intradermal skin tests, remain controversial.^{21,30,31} Thus, it is important to explore the risk factors of oxaliplatin-related HSR to establish an effective patient management strategy.

Little information is available about the risk factors of oxaliplatin-related HSR. To our knowledge, only 4 investigations have previously attempted to identify potential predictive factors by multivariate analysis.^{11–14} Kim et al^{12,13} analyzed the possible association between oxaliplatin-related HSR and clinical characteristics and found that younger patients, females, and patients receiving oxaliplatin in salvage regimens were more likely to experience oxaliplatin-related HSR. On the basis of multivariate analysis, Mori et al¹⁴ reported that being young and having an oxaliplatin-free interval were independent risk factors, whereas Shao et al¹¹ reported higher oxaliplatin dose per infusion as an independent risk factor. Moreover, a recent

study¹³ found that a lower dose of dexamethasone (<20 mg) could be a positive risk factor. In our study, all patients except one were taking the same dose of dexamethasone (6.6 mg) as premedication; however, the aforementioned variables that were previously reported as potential risk factors were not significant in our study. On the contrary, we found that high levels of eosinophil in peripheral blood and being male were independent risk factors for oxaliplatin-related HSR. Eosinophil, a type of immune cell, is considered to mediate allergic responses, so in patients with high eosinophil counts certain mechanisms may exist for HSR to oxaliplatin.

It is clear that among all these studies, including the study being presented here, there is no risk factor that has been identified consistently enough to make it a reliable and definite risk factor for HSR. The observed differences in these studies may result, in part, not only from the ethnic differences of participants but also from differences in the research design. Moreover, all studies were based on a retrospective design, so some medical records may have been insufficient or inadequate. To resolve these problems, more large-scale clinical studies based on a prospective design are needed.

The tolerable rechallenge of oxaliplatin after a patient has developed an HSR can be problematic, and various approaches, such as using prophylactic agents (eg, corticosteroids and antihistamines), extending administration time, and using desensitization procedures, are currently being used with varied results. As for the modified premedication approach using prophylactic agents, Shibata et al¹⁰ reported that 8 (72.7%) of 11 patients who experienced a grade 1 or 2 oxaliplatin-related HSR underwent tolerable oxaliplatin readministration with prophylactic agents. Siu et al²⁸ readministered oxaliplatin using prophylactic agents in 14 patients who had developed grade 1/2 HSRs, and 10 cases (71.4%) were successful. On the other hand, Brandi et al⁵ reported that only 1 (16.7%) of 6 patients was successful and the other patients (83%) developed HSRs again when oxaliplatin was readministered with prophylactic agents. In our study, modified premedication with prophylactic agents was effective in 2 (28.6%) of 7 patients who successfully completed their oxaliplatin-based treatment. Rechallenging oxaliplatin using prophylactic agents may be feasible if their use is limited to patients who developed grade 1/2 (not grade 3/4)

HSRs. Although urgently needed, there is no standardized protocol available for premedicating patients to prepare them for rechallenging oxaliplatin.

As for desensitization procedures, findings from several studies are encouraging. Although these studies involved a relatively small sample (1–3 patients), most reports had a 100% success rate using desensitization procedures to rechallenge oxaliplatin.^{23–25,32} Cortijo-Cascajares et al²¹ readministered oxaliplatin using desensitization protocols in 21 patients who had developed grade 2 (67%) or grade 3 (33%) HSRs, and 89% of these patients did not develop a new HSR. Although new HSRs of mild severity occurred in 11% patients, none of the cases were severe enough to warrant the cessation of treatment, and all patients completed the desensitization protocols. In our study, desensitization protocol was administered to 3 patients who had developed grade 2 (1 patient) or grade 3 (2 patients) HSRs, and all patients successfully completed their oxaliplatin-based treatments. These results seem promising, and we are surmising that desensitization procedures may be useful in rechallenging oxaliplatin not only in patients with grade 1/2 HSRs but also in those with grade 3 HSRs. However, in deciding whether to use desensitization procedures, the potential benefits of rechallenging patients with oxaliplatin should be weighed against the risks of patients developing new HSR.

As discussed above, there are several encouraging reports about procedures to desensitize patients to oxaliplatin, but the desensitization protocols used in these studies are varied in terms of the prophylactic agents used, infusion time, and the administration of increasing concentrations of oxaliplatin. For the tolerable readministration of oxaliplatin and the prevention of life-threatening anaphylactic reactions, a standard desensitization protocol is needed. Although it is possible that the maximum blood concentration level of oxaliplatin can be reduced with a desensitization protocol, it is still doubtful whether this will result in decreased antitumor activity.¹⁷ Therefore, this makes it necessary to validate the efficacy of desensitization protocols for HSR.

CONCLUSION

In conclusion, this retrospective study was conducted to clarify the risk factors for oxaliplatin-related HSR and the efficacy of the desensitization protocol. Our findings suggest that being male and having high levels

of peripheral eosinophil may increase the risk of HSR. Unfortunately, our results do not concur with risk factors suggested in other reports; therefore, among the studies performed to date (including our own), there is still no consensus on the risk factors for HSR.

In addition, although our results suggest that desensitization procedures could be an effective treatment option for oxaliplatin-related HSR, a standard protocol that is optimized in terms of efficacy and tolerability still needs to be established so that treatment procedures can be replicated for more consistent results.

ACKNOWLEDGMENTS

We thank the all members of Medical Oncology, Kyoto Prefectural University Hospital.

CONFLICTS OF INTEREST

Eigo Otsuji is affiliated with a donation-funded department of Yakult Co. Ltd. The other authors have no conflict of interest to declare.

REFERENCES

- Mathé G, Kidani Y, Segiguchi M, et al. Oxalato-platinum or 1-OHP, a third-generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum. *Biomed Pharmacother*. 1989;43:237–250.
- Goldberg R. N9741: a phase III study comparing irinotecan to oxaliplatin-containing regimens in advanced colorectal cancer. *Clin Colorectal Cancer*. 2002;2:81.
- 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.
- Gowda A, Goel R, Berdzik J, et al. Hypersensitivity reactions to oxaliplatin: incidence and management. *Oncology*. 2004;18:1671–1675. discussion 1676, 1680, 1683–1674.
- Brandi G, Pantaleo MA, Galli C, et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer*. 2003;89:477–481.
- Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol*. 2009;102:179–187. quiz 187–179, 222.
- Sato J, Terui K, Hayakari M. Effect of preliminary medication on oxaliplatin hypersensitivity. [in Japanese]. *Gan To Kagaku Ryoho*. 2009;36:1125–1129.
- Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol*. 1999;17:1141.
- Koren C, Yerushalmi R, Katz A, et al. Hypersensitivity reaction to cisplatin during chemoradiation therapy for gynecologic malignancy. *Am J Clin Oncol*. 2002;25:625–626.
- Shibata Y, Ariyama H, Baba E, et al. Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan. *Int J Clin Oncol*. 2009;14:397–401.
- Shao YY, Hu FC, Liang JT, et al. Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc*. 2010;109:362–368.
- Kim BH, Bradley T, Tai J, Budman DR. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology*. 2009;76:231–238.
- Kim MY, Kang SY, Lee SY, et al. Hypersensitivity reactions to oxaliplatin: clinical features and risk factors in Koreans. *Asian Pacific journal of cancer prevention: APJCP*. 2012;13:1209–1215.
- Mori Y, Nishimura T, Kitano T, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology*. 2010;79:136–143.
- Rosa DD, Ismael GF, de Azambuja E, et al. OPTIMOX1 in advanced colorectal cancer: lack of evidence for a stop-and-go strategy. *J Clin Oncol*. 2006;24:5176–5177. author reply 5177.
- Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol*. 2006;24:394–400.
- de Gramont A, Buyse M, Abrahantes JC, et al. Reintroduction of oxaliplatin is associated with improved survival in advanced colorectal cancer. *J Clin Oncol*. 2007;25:3224–3229.
- Siu SW, Chan WL, Liu KY, et al. Re-challenging patients with oxaliplatin allergy: the successful use of a standardised pre-medication protocol in a single institute. *Clin Oncol*. 2011;23:558–559.
- Kidera Y, Satoh T, Ueda S, et al. High-dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified FOLFOX6 from hypersensitivity reactions induced by oxaliplatin. *Int J Clin Oncol*. 2011;16:244–249.
- O'Cearbhaill R, Zhou Q, Iasonos A, et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. *Gynecol Oncol*. 2010;116:326–331.
- Cortijo-Cascajares S, Nacle-Lopez I, Garcia-Escobar I, et al. Effectiveness of oxaliplatin desensitization protocols. *Clin Transl Oncol*. 2013;15:219–225.
- Syrigou EI, Karapanagiotou EM, Alamara CV, et al. Hypersensitivity reactions to oxaliplatin: a retrospective study and the development of a desensitization proto-

- col. *Clin Colorectal Cancer*. 2009;8:106–109.
23. Rosique-Robles D, Vicent Verge JM, Borrás-Blasco J, et al. Successful desensitization protocol for hypersensitivity reactions caused by oxaliplatin. *Int J Clin Pharmacol Ther*. 2007;45:606–610.
 24. Edmondson DA, Gruling BJ, Urmanski AM, et al. Oxaliplatin hypersensitivity: case report and successful repeat desensitization. *Am J Ther*. 2007;14:116–118.
 25. Nozawa H, Muto Y, Yamada Y. Desensitization to oxaliplatin with two stages of premedication in a patient with metastatic rectal cancer. *Clin Ther*. 2008;30:1160–1165.
 26. Andre T, Tournigand C, Achille E, et al. Adjuvant treatment of colon cancer MOSAIC study's main results [in French]. *Bull Cancer*. 2006;93(Suppl 1):S5–S9.
 27. Rose PG, Fusco N, Smrekar M, et al. Successful administration of carboplatin in patients with clinically documented carboplatin hypersensitivity. *Gynecol Oncol*. 2003;89:429–433.
 28. Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol*. 2006;17:259–261.
 29. Polyzos A, Tsavaris N, Gogas H, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology*. 2009;76:36–41.
 30. Garufi C, Cristaudo A, Vanni B, et al. Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol*. 2003;14:497–498.
 31. Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol*. 2003;21:4611–4614.
 32. Mis L, Fernando NH, Hurwitz HI, Morse MA. Successful desensitization to oxaliplatin. *Ann Pharmacother*. 2005;39:966–969.

Address correspondence to: Takeshi Ishikawa, MD, PhD, 465 Kajii-cho, Kawaramachi-hirokoji, Kamigyo-ku, Kyoto-city, Kyoto prefecture, Japan 602-8566. E-mail: iskw-t@koto.kpu-m.ac.jp