

Incidence and Risk of Oxaliplatin-Induced Hypersensitivity in Patients with Asymptomatic Prior Exposure: A Prospective Observational Study



Kyoung-Hee Sohn, MD^{a,b}, Dong-Yoon Kang, MD^c, Ju-Young Kim, MD^d, Suh-Young Lee, MD^{a,b},
Kyung-Hun Lee, MD, PhD^{a,e}, Sae-Won Han, MD, PhD^{a,e}, and Hye-Ryun Kang, MD, PhD^{a,b,c} Seoul, Korea

What is already known about this topic? The wide use of oxaliplatin in clinical practice has led to an increased incidence of oxaliplatin-induced hypersensitivity reactions (HSRs).

What does this article add to our knowledge? In this prospective study, we observed that patients with previous exposure to oxaliplatin experienced earlier HSR onset and more severe and frequent HSR episodes. A history of asymptomatic exposure to oxaliplatin and a longer oxaliplatin-free interval were independent risk factors for HSRs.

How does this study impact current management guidelines? Clinicians should pay attention to the risk of oxaliplatin HSRs among patients with a history of asymptomatic exposure to oxaliplatin, especially if re-exposure occurs after an oxaliplatin-free interval of more than 3 years.

BACKGROUND: Oxaliplatin-related hypersensitivity reactions (HSRs), which can be life threatening, have introduced a dilemma regarding the use of chemotherapeutic agents. Because repeated exposure to oxaliplatin may increase the risk of sensitization, patients with a history of prior asymptomatic exposure require risk-stratified care.

OBJECTIVE: This study aimed to elucidate the incidence and risk of oxaliplatin HSRs in patients with a history of asymptomatic prior exposure.

METHODS: We performed a prospective observational study of patients who completed oxaliplatin-based chemotherapy between March 2013 and January 2015. Prior exposure to oxaliplatin, the oxaliplatin-free interval, reaction severity, eosinophil counts, and premedication were reviewed to assess the risk factors.

RESULTS: A total of 793 patients were enrolled, among whom 148 (18.7%) experienced an HSR. The HSR incidence was 15.2% among oxaliplatin-naïve patients but increased to 31.9% among those with a history of asymptomatic exposure and 75.0% among those with a history of oxaliplatin HSRs during the previous exposure, despite prophylaxis. The mean HSR onset cycle was earliest in the previous HSR group, followed by the previous asymptomatic exposure and nonexposure groups. The HSR severity also differed according to the previous exposure history and HSRs. In the multivariate analysis, prior exposure to oxaliplatin (odds ratio [OR], 3.78; 95% confidence interval [CI], 2.46–5.79) and a longer oxaliplatin-free interval (≥ 36 months; OR, 4.85; 95% CI, 1.60–14.37) were independent risk factors for HSRs.

CONCLUSIONS: Previous exposure to oxaliplatin is a risk factor for earlier HSR onset and more severe and frequent HSR episodes, even if prior therapy was well tolerated. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1642-8)

Key words: Oxaliplatin; Hypersensitivity; Drug hypersensitivity; Prospective studies

^aDepartment of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

^bInstitute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul National University College of Medicine, Seoul, Korea

^cSeoul National University Hospital Regional Pharmacovigilance Center, Seoul, Korea

^dDepartment of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon, Korea

^eCancer Research Institute, Seoul National University Hospital, Seoul, Korea
No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 20, 2017; revised manuscript received and accepted for publication December 15, 2017.

Available online February 14, 2018.

Corresponding author: Hye-Ryun Kang, MD, PhD, Seoul National University Hospital, 101 Daehak-ro, Jongno-Gu, Seoul 110-744, Korea. E-mail: helenmed@snu.ac.kr

2213-2198

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<https://doi.org/10.1016/j.jaip.2017.12.026>

Oxaliplatin, a third-generation platinum agent, is a standard treatment option for gastrointestinal malignancies that is usually administered in combination with fluorouracil and leucovorin (FOLFOX regimen) for colorectal cancer¹ or with capecitabine (XELOX regimen) for advanced gastric or colorectal cancer.^{2,3} However, oxaliplatin-induced hypersensitivity reactions (HSRs) are reported in 8.9% to 24.3% of cases, and are severe in approximately 1% to 3% of cases.⁴⁻⁷ Oxaliplatin HSRs range in severity from mild pruritus or urticaria to a fatal anaphylactic reaction.^{8,9} Therefore, the precise prediction and optimal management of HSRs are clinically important for patients treated with oxaliplatin.

Abbreviations used
OR- Odds ratio
CI- Confidence interval
HSR- Hypersensitivity reaction
FOLFOX- Folinic acid, fluorouracil, and oxaliplatin
XELOX- Capecitabine and oxaliplatin

Currently, the risk of re-exposure to oxaliplatin is increasing because gastrointestinal malignancies have increased along with population aging, and advances in medical technology have improved the survival rates of patients with cancer. Cyclic exposure to oxaliplatin increases the risk of sensitization and specific IgE production¹⁰; however, the former usually occurs without symptom development (ie, silent sensitization).¹¹ If sensitized patients are re-exposed to oxaliplatin, however, allergic symptoms will eventually manifest. Therefore, oxaliplatin HSR risk stratification should be performed to establish an individualized optimal strategy for high-risk patients who were previously exposed to oxaliplatin.

Herein, we describe a prospective observational study of patients who received oxaliplatin-based chemotherapy. In this study, we assessed the incidence, severity, and risk factors of oxaliplatin HSRs according to the previous oxaliplatin exposure status.

METHODS

Patients

A total of 793 patients who underwent FOLFOX or XELOX chemotherapy were recruited among patients who began and completed an oxaliplatin-based chemotherapy regimen between March 2013 and January 2015 at Seoul National University Hospital. Institutional review board approval was obtained for this study (IRB No.: 1301-118-461), and all patients provided written informed consent to participate in this research.

The patients' demographic data, type of cancer, previous history of oxaliplatin exposure, purpose of chemotherapy, and premedication use were thoroughly reviewed by pharmacovigilance nurses. The occurrence of an HSR and its clinical manifestations were investigated by phone interviews 1 day after oxaliplatin injections, as well as through a complete review of the medical records. HSR severity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE).¹⁰

The study patients were divided into 3 subgroups according to their history of previous oxaliplatin exposure or HSRs: group 1 comprised oxaliplatin-naïve patients with no history of oxaliplatin exposure, group 2 those with previous asymptomatic exposure to oxaliplatin, and group 3 those with a history of oxaliplatin-induced HSRs during a previous exposure (Figure 1).

Oxaliplatin-containing chemotherapy regimen

The following protocols were used to provide either adjuvant or palliative treatment for gastric cancer and colorectal cancer. FOLFOX comprised biweekly oxaliplatin 85 mg/m², leucovorin 200 mg/m², and 5-FU 1000 mg/m². XELOX comprised oxaliplatin 130 mg/m² and capecitabine 4000 mg/m² every 3 weeks. During the seventh cycle and thereafter, chlorpheniramine 4 mg, hydrocortisone 100 mg, and an H₂ antagonist were administered as premedication 1 hour before oxaliplatin administration to prevent oxaliplatin-induced HSRs, because it has been widely suggested that an HSR to

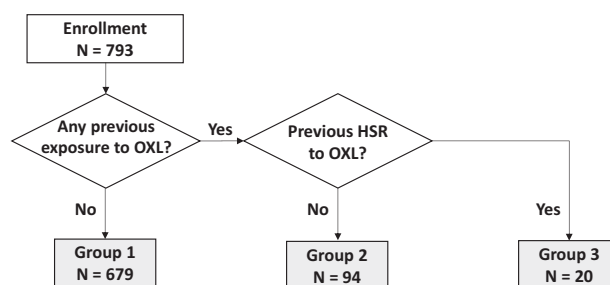


FIGURE 1. Flowchart of study population. HSR, Hypersensitivity reaction; OXL, oxaliplatin.

oxaliplatin occurs mainly after the seventh infusion.¹² If patients experienced moderate-to-severe emesis, dexamethasone 20 mg was additionally administered.

Statistical method

The statistical analyses used were χ^2 test or Fisher's exact test for the categorical variables of sex, age group, prior oxaliplatin exposure, cancer type, cancer treatment goal, and HSR. We used a χ^2 test for a linear trend to compare the incidence among 3 groups and a χ^2 test to compare each two groups. Levene's tests of homogeneity of variances were first performed to confirm the normal distribution between groups. A 1-way analysis of variance with the Bonferroni correction was used to compare the mean cycles and oxaliplatin-free intervals among the 3 groups. The independent Student's *t*-test and Mann-Whitney *U* test were performed as appropriate to compare the oxaliplatin-free interval and oxaliplatin cumulative dose according to the occurrence of HSRs.

A multivariate logistic regression model was applied for the risk factor evaluation. Together with sex and age, all variables with a *P* value < .1 in the univariate analysis were included as candidate variables in the multiple logistic regression. The results were considered significant if the 2-sided *P* value was < .05. The oxaliplatin-free interval times were calculated from the last date of prior exposure to oxaliplatin and were censored for patients who had not developed an HSR at the last follow-up. The oxaliplatin-free interval and HSR were assessed using the Kaplan-Meier method. Statistical analyses were performed using SPSS software (version 23.0; SPSS, Chicago, Ill).

RESULTS

Study subjects

The patients' baseline characteristics are listed in Table I. The mean age was 59.0 (± 10.8) years, and 481 (60.7%) were male. Colorectal cancer (67.0%) was the most common therapeutic indication, followed by gastric cancer (31.9%) and pancreatic or liver cancer (1.0%). Oxaliplatin was administered to 464 patients (58.5%) for adjuvant chemotherapy and 329 patients (41.5%) for palliative treatment. One hundred fourteen patients (34.7%) had been exposed to oxaliplatin previously, including 20 patients with a history of previous oxaliplatin HSRs. Regarding the chemotherapy regimen, 63.7% of patients received XELOX and 36.1% received FOLFOX.

Oxaliplatin HSR incidence and severity

The overall incidence of an HSR was 18.7%. Among oxaliplatin-naïve patients (group 1), only 15.2% experienced an

TABLE I. Baseline characteristics of study populations

Age, y	59.0 ± 10.8
Sex, male (%)	481/793 (60.7%)
Type of cancer	
Colorectal	531/793 (67.0%)
Gastric cancer	254/793 (31.9%)
Others*	8/793 (1.0%)
Purpose of chemotherapy	
Adjuvant	464/793 (58.5%)
Palliative	329/793 (41.5%)
Previous OXL exposure (–)	215/329 (65.3%)
Previous OXL exposure (+)	114/329 (34.7%)
Chemotherapy regimen	
FOLFOX	286/793 (36.1%)
XELOX	505/793 (63.7%)
FOLFIRINOX 1	1/793 (0.1%)
TS-1 + OXL 1	1/793 (0.1%)
Eosinophil count (per μ L)	174.1 ± 165.9

FOLFIRINOX, Folinic acid, fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; TS-1 + OXL, TS-1 and oxaliplatin; XELOX, capecitabine and oxaliplatin.

*Pancreatic cancer 7, hepatocellular carcinoma 1.

HSR; in contrast, 39.5% of patients with prior exposure to oxaliplatin developed an HSR ($P = .003$). Within the latter group, HSRs developed in 31.9% of the previous asymptomatic exposure group (group 2), and 75.0% of those with HSRs during a previous exposure (group 3, 15/20) experienced recurrent HSRs on re-exposure to oxaliplatin. A linear increasing trend was observed from group 1 to group 3 (Figure 2, A).

The severity of HSRs also differed among the groups. Those in group 1 developed much milder HSRs, compared with those in groups 2 and 3 (mean grades: 1.7 ± 0.1 , 2.2 ± 0.1 , and 2.93 ± 0.7 , respectively, P for linear trend $<.001$). Particularly, only 2% of patients in group 1 developed grade 4 HSR, compared with 17% and 27% in groups 2 and 3, respectively. In addition, the mean cycle of onset differed significantly among the groups. The oxaliplatin-naïve group (group 1) had a relatively later onset (4.72 ± 2.73 cycles), compared with group 2 (2.71 ± 1.90 cycles) and group 3 (2.18 ± 2.72 cycles) ($P < .001$) (Figure 2, B).

Regarding chemotherapy regimen, the rate of HSRs was 30.4% (87/286) in the FOLFOX group and 12.1% (61/505) in the XELOX group ($P < .001$). Although the regimen groups differed significantly with regard to the cycle of onset ($P = .01$), the cumulative dose did not differ significantly (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Clinical decision regarding further cycles after oxaliplatin HSRs

Except for 1 patient who ceased oxaliplatin treatment at his own discretion, 147 of 148 patients with oxaliplatin-induced HSRs continued oxaliplatin treatment. The prevention strategies used during the following cycle differed according to the severity of HSRs (Table II). Among patients with milder HSRs, the oxaliplatin completion rate without premedication was 80.0% for those with grade 1 HSRs, but only 37.5% for those with grade 2 HSRs ($P = .004$). Premedication was administered

to 43 patients with grade 2 HSRs, and 41 (95.3%) patients completed the oxaliplatin-containing chemotherapy course without HSRs. In contrast, the premedication success rate among patients with grade 3 HSRs was only 50.0% (5/10). Twenty-one of 31 patients with grade 3 and 4 HSRs underwent desensitization to oxaliplatin during the cycle after their first HSR, which yielded success rates of 90.0% (9/10) and 90.0% (10/11) for patients with grade 3 and grade 4 HSRs, respectively.

Risk factors for the development of oxaliplatin-induced HSR

We next used a stratified multivariable logistic regression analysis to explore potential risk factors that might influence the development of oxaliplatin-induced HSR (Table III). Because group 3 (previous HSR group) had already used premedication, they were excluded from the analysis. After adjusting for age, sex, purpose of chemotherapy, previous exposure, oxaliplatin-free interval, eosinophil counts, and total cumulative dose, 3 parameters were identified as risk factors for HSRs.

The risk of oxaliplatin-induced HSR development increased significantly among patients with previous asymptomatic exposure (group 2) (odds ratios [OR] = 3.78; 95% confidence interval [CI], 2.46–5.79; $P < .001$). To facilitate the interpretation of this result, we used Kaplan-Meier curves to define clinically meaningful cutoff values for the oxaliplatin-free interval. The oxaliplatin-free interval versus HSR graph indicated a peak HSR incidence at 42 to 54 months after the previous exposure to oxaliplatin (Figure 3, A). In a multivariable logistic regression using an average time interval, patients with an oxaliplatin-free interval >36 months had a higher risk of HSRs compared with those with an oxaliplatin-free interval <36 months (OR = 4.85; 95% CI, 1.60–14.37; $P = .004$). In this comparison, the oxaliplatin-free interval was significantly longer in the HSR group than in the non-HSR group (mean: 21.6 ± 19.7 months vs 16.8 ± 20.5 months, $P = 0.007$) (Figure 3, B). This tendency was also found in group 3 (free interval for the HSR group was 20.7 ± 13.7 months and for the non-HSR group, 16.2 ± 13.8 months), but this was not statistically significant using the nonparametric Mann-Whitney U test. In contrast, the risk of HSRs decreased slightly as the cumulative dose increased in the oxaliplatin-naïve group (OR = 0.998, $P < .001$).

Clinical course of oxaliplatin-induced anaphylaxis

We also assessed the clinical characteristics of 11 patients with oxaliplatin-induced anaphylaxis (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Eight patients (72.7%) had received antihistamine and corticosteroid premedication during the cycle in which anaphylaxis occurred. Anaphylaxis first occurred during the second cycle in 72.7% of the patients. Accordingly, 10 patients (90.9%) underwent desensitization, and all successfully completed the oxaliplatin infusion. One patient who developed anaphylaxis in the absence of preventive prophylaxis before oxaliplatin chemotherapy received a slow infusion with antihistamine and corticosteroid premedication instead of desensitization and completed infusion without recurrent HSRs.

DISCUSSION

To the best of our knowledge, this is the first and largest prospective study of immediate oxaliplatin-induced hypersensitivity. As a result, we determined oxaliplatin HSR incidence rates

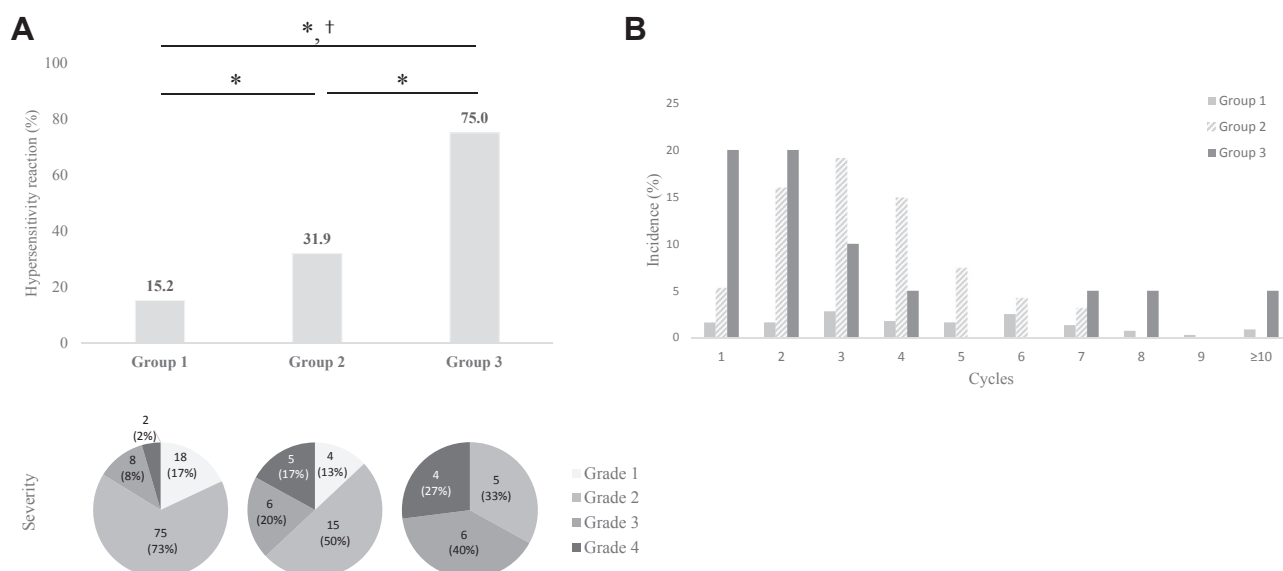


FIGURE 2. A, Bar graph demonstrating an increasing trend of incidence of HSR and pie charts presenting increasing severity of HSR across the groups. An asterisk (*) indicates that P value $<.05$ between 2 groups using the χ^2 test and a dagger (†) indicates that P value $<.001$ among 3 groups by the χ^2 test for a linear trend. B, The incidence of first oxaliplatin HSR depending on chemotherapy cycles. HSR, Hypersensitivity reaction.

TABLE II. Clinical decision at the following cycle after oxaliplatin HSR according to the grade of HSR

Grade	No treatment (N)/success rate* (%)		Premedication (N)/success rate (%)		Desensitization (N)/success rate (%)	
1	15	80.0	7	100	—	—
2	48	37.5	43	95.3	3	100
3	—	—	10	50.0	10	90.0
4	—	—	—	—	11†	90.9

HSR, Hypersensitivity reaction.

*Success was defined when oxaliplatin-containing chemotherapy continued with current prevention measure for hypersensitivity.

†One patient completed the full period of oxaliplatin administration at lower infusion rate with premedication.

of 15.2%, 31.9%, and 75.0% in the oxaliplatin-naïve group, oxaliplatin re-exposure group, and previous HSR group, respectively, with an overall average of 18.7%. We found that previous asymptomatic exposure to oxaliplatin and an oxaliplatin-free interval of approximately 3 to 5 years were independent risk factors for the development of HSRs. In addition, 11 patients with oxaliplatin-induced anaphylaxis developed severe allergic reactions despite receiving concomitant prophylactic premedication.

The mechanism underlying oxaliplatin HSRs is almost always IgE mediated, although occasional patients can have cytokine storm.¹²⁻¹⁴ Previous studies have suggested associations of IgE-mediated type 1 hypersensitivity with oxaliplatin HSRs.^{12,13} The fact that oxaliplatin-induced HSRs usually occur after several exposures and present immediately after the infusion suggests a type 1 hypersensitivity reaction caused by the degranulation of mast cells in response to IgE induced by sensitization to oxaliplatin. The characteristic symptoms and positive skin tests^{8,14} also support type 1 hypersensitivity as a pathomechanism. Another hypothesis suggests that oxaliplatin may act as a superantigen by binding directly to major histocompatibility complex class II receptors on antigen-presenting cells, leading to T-lymphocyte activation and

TABLE III. Multivariate logistic regression analyses for hypersensitivity reactions

	Adjusted odds ratio	95% Confidence interval	P value*
Age	1.01	0.97-1.06	.497
Sex	1.34	0.53-3.50	.579
Chemotherapy regimen	1.22	0.46-3.28	.691
Previous asymptomatic exposure to oxaliplatin	3.78	2.46-5.80	<.001
Oxaliplatin-free interval			
<36 mo	Reference		
≥36 mo	4.85	1.60-14.37	.005
Eosinophil counts	0.81	0.47-1.42	.305
Oxaliplatin cumulative dose			
Exposure (—)	0.998	0.998-0.999	.001
Exposure (+)	1.000	0.999-1.000	.174

*Adjusted factors for multiple logistic regression: age, sex, regimen of chemotherapy, previous exposure, free interval, eosinophil counts, and total cumulative dose.

massive cytokine release.¹⁵ In our study, the occurrence of HSRs in one-third of patients in the previous asymptomatic exposure group (group 2) further suggests that silent

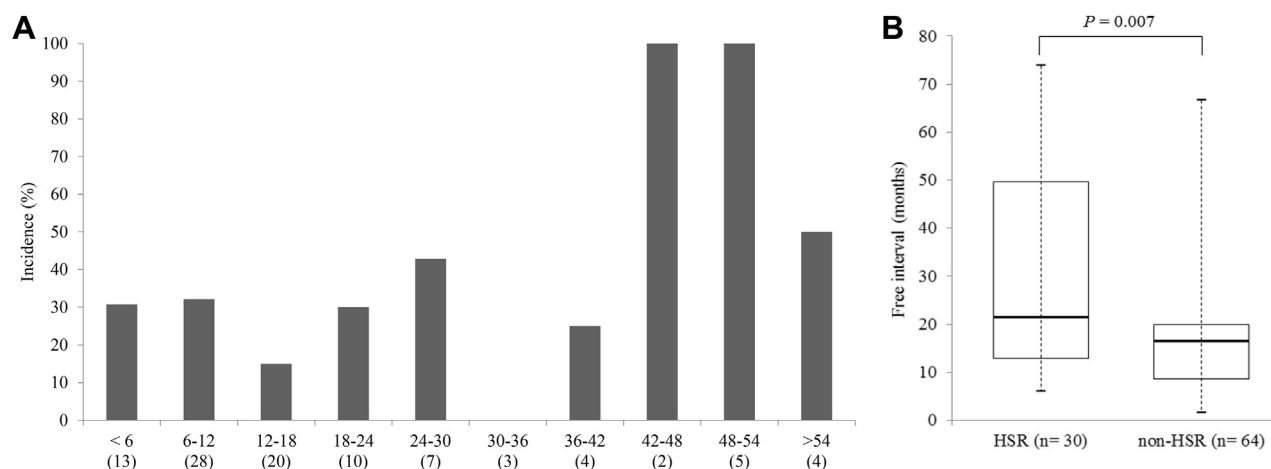


FIGURE 3. **A**, The incidence of hypersensitivity reaction according to the oxaliplatin-free interval between chemotherapy in group 2. **B**, The box plot for the free interval between HSR and non-HSR in group 2. The lower and upper edges of each box represent the 25th and 75th centile of observed data, respectively. The line partitioning box corresponds to median observation. Incidence rate means the number of patients with HSR during a given time interval. HSR, Hypersensitivity reaction.

sensitization via repeated exposure is a crucial step underlying the occurrence of HSRs.

Previous asymptomatic oxaliplatin exposure and a long oxaliplatin-free interval were identified as important risk factors for the development of oxaliplatin-induced HSRs. In patients with previous exposure to oxaliplatin or a previous history of oxaliplatin HSRs, HSRs occurred during earlier cycles and with more severe symptoms. In our hospital, patients receiving oxaliplatin-containing chemotherapy were routinely administered premedication comprising hydrocortisone 100 mg, an antihistamine, and a H_2 antagonist after the seventh cycle for prophylaxis against a potential HSR. Therefore, this premedication may have prevented HSRs after the seventh cycle. Other previous studies of the risk factors for oxaliplatin-induced HSRs reported varying results. One reported a higher risk among women,¹⁶ whereas another reported a higher risk among men,¹⁷ and a third study identified younger age as a risk factor.¹⁸ In this study, although the multivariate and subgroup analyses were stratified by age and sex, no significant differences were observed. Previous studies also identified the eosinophil count¹⁷ and lactate dehydrogenase level¹⁹ as risk factors; however, the eosinophil counts showed no significance in this study.

Our study showed a significant difference in HSR incidence between the FOLFOX group (30.4%) and the XELOX group (12.1%). In the FOLFOX group, oxaliplatin was administered once every 2 weeks, whereas in the XELOX group, oxaliplatin was administered every 3 weeks with a 1.53 times larger dose per cycle compared with the FOLFOX group. However, there was no difference between the 2 groups in cumulative dose or on multivariate analysis for HSRs, which suggests that the observed differences in the incidence and onset cycle when HSRs developed between the 2 groups were caused by the differences in oxaliplatin dose per cycle and the intervals between cycles. Therefore, although oxaliplatin-related HSRs are known to frequently develop after the seventh cycle, physicians should pay attention to the probability of HSRs in earlier cycles when patients receive oxaliplatin as part of a XELOX regimen.

Interestingly, we confirmed that the risk of oxaliplatin HSRs increased with a longer oxaliplatin-free interval, particularly after 36 months. Once oxaliplatin-specific IgE has been induced via sensitization, it can contribute to the intensity of HSRs by enhancing the functions of FcεRI, an IgE receptor expressed on mast cells and basophils.^{20,21} Similar to our results, 1 previous study reported that patients who received repeated carboplatin therapy ≥ 12 months after the initial exposure faced increased risks of HSRs and severe HSRs.²² In our study, we had a limited number of patients with HSRs with an oxaliplatin-free interval greater than 5 years because few patients resumed chemotherapy after 5 years because a considerable number of patients already had a recurrence within 5 years, and most patients in complete remission after 5 years did not need additional chemotherapy. Further studies are needed to define the re-exposure timing at the highest risk of an HSR to oxaliplatin among patients with asymptomatic previous exposure.

Although the immune response wanes during a long drug-free interval after the completion of a previous chemotherapy regimen, re-exposure to oxaliplatin could promptly activate the memory response, leading to the development of an immediate HSR on the next exposure. This concept is supported by the observed peak HSR onset during the second cycle in group 2.

Oxaliplatin rechallenge should be considered carefully in patients with a prior history of oxaliplatin HSRs. It is recommended to perform desensitization if a given drug is the patient's only option to treat a life-threatening disease, with appropriate informed consent. In this study, 10 of 11 patients with oxaliplatin-induced anaphylaxis completed oxaliplatin treatment via desensitization. However, 1 patient who developed anaphylaxis in the absence of prophylactic premedication safely underwent subsequent oxaliplatin treatments administered via slow infusion with premedication.

Premedication with steroids and antihistamines is not entirely sufficient to prevent HSRs.²³ In the present study, 50.0% (5/10) of the patients experienced grade 3 HSR in the following cycle, despite receiving premedication, and eventually underwent desensitization. Furthermore, prophylactic premedication cannot

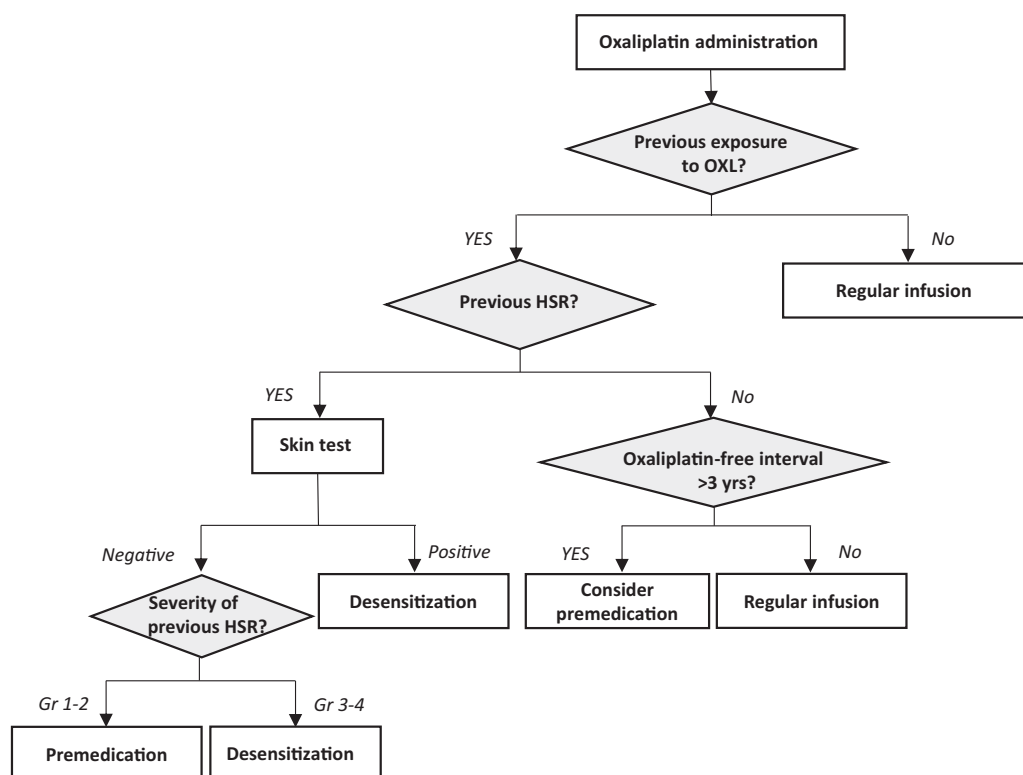


FIGURE 4. Clinical decision-making flowchart for predicting oxaliplatin HSR with risk stratification. *HSR*, Hypersensitivity reaction; *OXL*, oxaliplatin.

prevent anaphylaxis. In this study, 8 of 11 patients who experienced oxaliplatin-induced anaphylaxis had severe allergic reactions despite receiving prophylactic premedication (antihistamines and corticosteroids). Most had a previous oxaliplatin exposure history, suggesting that different strategies should be employed with regard to the individual risk factor. As the mechanism of oxaliplatin HSRs appears to be related to type 1 allergic hypersensitivity, desensitization appears to be the optimal strategy for preventing recurrent HSRs. In our previous study, 89.5% of the desensitized patients completed oxaliplatin infusion without any HSR symptoms, regardless of the severity of HSR.²⁴ In this study, we found that previous exposure to oxaliplatin and a long oxaliplatin-free interval are strong risk factors for oxaliplatin HSRs and provided an algorithm for predicting oxaliplatin hypersensitivity with risk stratification (Figure 4).

Skin testing results were found to have a high positive predictive value regarding HSR development, and have therefore been recommended to predict the risk of oxaliplatin HSRs or to determine the infusion rate during the desensitization protocol.²⁵⁻²⁷ The sensitivity of the platinum agent skin test ranges from 59% to 77%, with a negative predictive value of 93% to 95%.^{28,29} Previous skin test results suggest that patients with previous oxaliplatin exposure and a long oxaliplatin free-interval should undergo a standardized skin test to predict the likelihood of oxaliplatin HSRs. Other recent studies reported that a basophil activation test successfully used platinum-specific IgE to predict the outcomes of desensitization.³⁰ Further studies are needed to establish each individual therapeutic strategy.

In this prospective observational study, we determined the incidence of HSRs among patients who were treated via

oxaliplatin-based chemotherapy. We must note a few limitations. First, a skin test was performed in part for the evaluation of oxaliplatin HSRs in this study. Second, the incidence and severity of HSRs might have been underestimated because of the routine administration of premedication, including antihistamines and steroids, after the seventh cycle. Nevertheless, this was the first prospective study of HSRs among representative patients treated with oxaliplatin, and it reliably validates the incidence of and risk factors for oxaliplatin HSRs.

In conclusion, patients with previous asymptomatic exposure to oxaliplatin are at risk of developing more frequent and severe HSRs during earlier cycles. Prior exposure to oxaliplatin and a long oxaliplatin-free interval were identified as risk factors predictive of the development of oxaliplatin HSRs. Therefore, clinicians should pay attention to each patient's history of prior exposure to oxaliplatin and the oxaliplatin-free interval.

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TABLE E1. Patients' information according to the chemotherapy regimen

	FOLFOX (n = 286)	XELOX (n = 505)	P value
HSR incidence (%)	30.4%	12.1%	<.001
Grade 1	16.1%	14.5%	.636
Grade 2	59.9%	69.4%	.198
Grade 3	13.8%	12.9%	.927
Grade 4	10.3%	3.2%	.201
Cumulative dose (mg)	482 ± 384	490 ± 305	.546
Onset of cycles	4.53 ± 2.87	2.87 ± 2.02	.010

FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; HSR, hypersensitivity reaction; XELOX, capecitabine and oxaliplatin.

The HSR incidence was higher in the FOLFOX group compared to the XELOX group. There was no difference in cumulative dose or in multivariate analysis for HSR but a significant difference in the cycles at the onset of HSR between the 2 groups, which might be attributed to the differences in oxaliplatin dose and the interval between cycles. *P* value is based on the χ^2 test (HSR incidence and grade) and the Student's *t*-test (cumulative dose and onset of cycle). Bold indicates statistical significance (*P* < .05).

TABLE E2. Detailed information of patients with oxaliplatin-induced anaphylaxis

Group	Sex/age	Prior exposure to oxaliplatin	HSR on prior exposure (Gr)	OXL-free interval (d)	Cycle/dose (mg)	Premedication before HSR*	Management on the following cycles
1	F/58	No	—	—	6/425	No	Desensitization (15 cycles)
1	M/58	No	—	—	2/130	No	Desensitization (10 cycles)
2	M/77	Yes	No	1187	7/680	Yes	Desensitization (14 cycles)
2	M/57	Yes	No	833	2/260	Yes	Desensitization (3 cycles)
2	M/51	Yes	No	585	2/170	Yes	Desensitization (6 cycles)
2	M/61	Yes	No	881	2/180	Yes	Desensitization (4 cycles)
2	M/70	Yes	No	699	3/255	No	Slow infusion with premedication (11 cycles)
3	F/72	Yes	Yes (Gr 1)	593	2/136	Yes	Desensitization (4 cycles)
3	F/62	Yes	Yes (Gr 1)	754	2/208	Yes	Desensitization (5 cycles)
3	M/64	Yes	Yes (Gr 2)	125	2/208	Yes	Desensitization (3 cycles)
3	F/64	Yes	Yes (Gr 2)	699	2/220	Yes	Desensitization (5 cycles)

HSR, Hypersensitivity reaction; OXL, oxaliplatin.

*H1 and H2 blocker + hydrocortisone 100 mg was administration before HSR.