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Clinical Analysis of Hypersensitivity Reactions to Oxaliplatin Among Colorectal Cancer Patients

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This study investigated the characteristics of oxaliplatin-induced hypersensitivity reactions (HSRs) and evaluated the efficacy of premedication for controlling HSRs among colorectal cancer patients. A retrospective study was performed on the clinical records of 291 patients with colorectal cancer in The Tenth People's Hospital of Shanghai from January 2008 to January 2016. Patients who experienced HSRs to oxaliplatin were compared with those who did not. A total of 291 colorectal cancer patients received oxaliplatin, with 39 (13.40%) experiencing HSRs. Oxaliplatin-free interval and premedication with dexamethasone and antihistamine were independent variables for oxaliplatin-related HSRs. Rechallenging patients with premedication was successful in 72.2% of the patients who successfully completed their treatment. Attention should be paid to patients with any prior exposure to oxaliplatin. Patients with grades 1 and 2 HSRs can successfully rechallenge with oxaliplatin and complete their treatment by premedication with dexamethasone and antihistamine.

Key words: Oxaliplatin; Hypersensitivity reaction (HSR); Colorectal cancer; Premedication

INTRODUCTION

Oxaliplatin (L-OHP) is a third-generation, platinum-based agent that has shown activity in a wide variety of tumor types, including colorectal, pancreatic, biliary, gastroesophageal, and gynecologic malignancies[1]. Oxaliplatin-based regimens, including m-FOLFOX6 and Xelox, are currently standard treatments for colorectal cancer. The dose-limiting toxicities of L-OHP are cumulative sensory peripheral neuropathy[2], whereas hypersensitivity reactions (HSRs) have been recognized as severely problematic with the increasing use of oxaliplatin in clinical practice. The exact mechanism of oxaliplatin-induced HSRs remains unclear. Oxaliplatin-associated hypersensitivity usually occurs immediately after oxaliplatin administration, which suggests that oxaliplatin-related HSR is a type I, IgE-mediated[3] hypersensitivity. Rare cases of type II and type III reactions have also been reported. Type II reactions are associated with hemolysis and thrombocytopenia[4], whereas chronic urticaria, joint pain, and proteinuria indicate type III[5] reactions. The prevalence of type I, IgE-mediated HSR varies from 10.3%[6] to 20.2%[7] with diverse manifestations. Mild reactions present with itching and small-area erythema, and severe reactions include diffuse erythema, facial swelling, chest tightness, bronchospasm, and hypotension. HSRs may expose patients to the risk of severe symptoms, hospitalizations, or even death. Because oxaliplatin is one of the most frequently used drugs in the treatment of colorectal cancer, it is important to identify high-risk patients using oxaliplatin and manage HSRs in those patients. We retrospectively analyzed the prevalence, severity, risk factors, and premedication of HSRs among colorectal cancer patients being treated with oxaliplatin.

PATIENTS AND METHODS

Patients Selection

We enrolled 291 patients who were scheduled to receive oxaliplatin-based regimens in The Tenth People's Hospital of Shanghai in China from January 2008 to January 2016. All patients had histologically or cytologically confirmed colorectal adenocarcinoma. We retrospectively reviewed patients' records and collected data on baseline characteristics, such as age, gender, presence of preexisting allergies, and diagnosis. In addition, dose, rate, and interval of oxaliplatin administered, total number of oxaliplatin courses, premedication, and oxaliplatin-free interval were also collected.

Oxaliplatin-Free Interval

Patients were initially submitted to the oxaliplatin administration. Oxaliplatin was withdrawn due to the stop-and-go strategy or the completion of adjuvant

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chemotherapy, and then oxaliplatin was resumed at the time of disease progression.

Oxaliplatin-Based Chemotherapy

Two regimens were used for oxaliplatin-based adjuvant or palliative chemotherapy. FOLFOX was given once every 2 weeks, administered at 85 mg/m^2 of body surface area, and followed by leucovorin and fluorouracil. Xelox was given once every 3 weeks, administered at 130 mg/m^2 body surface area, and followed by capecitabine for 2 weeks.

Hypersensitivity Reactions

HSRs were assessed and classified according to the National Cancer Institute Common Criteria (NCI-CTCAE v4.0)[8]. An HSR score of 1 indicates transient flushing or rash, or drug fever <38°C; a score of 2 indicates rash, flushing, urticaria, dyspnea, or drug fever ≥38°C; a score of 3 indicates symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension; and a score of 4 indicates anaphylaxis.

Premedication Protocol

In April 2014, two patients experienced severe and life-threatening HSRs to oxaliplatin, manifested with coma and shock. From then on, to prevent HSRs during the oxaliplatin treatment, 10 mg of chlorpheniramine and 10 mg of dexamethasone were injected 1 h prior to the oxaliplatin administration in patients without contraindication to dexamethasone such as diabetes, gastric ulcer, among others. No H2 blockers were used. If patients experienced further HSRs despite premedication, another 10 mg of dexamethasone and 10 mg of chlorpheniramine would be administrated.

Statistical Method

All statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Logistic regression was used for the evaluation of risk factors. The risk factors examined included demographic data (gender and age), preexisting allergies, premedication (dexamethasone and antihistamine), total number of cycles, and oxaliplatin-free interval. Clinical data were compared between patients who experienced HSRs and those who did not. Results were considered significant with a two-sided value of $p<0.05$. For analysis, patients were categorized into two groups: the continuous group comprised people who had received oxaliplatin without break; the uncontinuous group comprised patients who had received oxaliplatin administration with an oxaliplatin-free interval. Cumulative incidence curves for HSR incidence according to number of treatment cycles delivered were estimated using the Kaplan–Meier method. The log-rank test was used to evaluate differences in the cumulative incidence curves of two groups.

RESULTS

The 291 patients who received their first cycle of FOLFOX or Xelox from January 2008 to January 2016 were identified and included for analysis. Demographics and baseline characteristics of patients are listed in Table 1. The mean age of the patients was 61.6 years (25–82 years), and the number of males was 173 (59.5%). Most patients (95%) had no prior history of allergic reactions; only 24 (8.2%) patients had prior allergic reactions to drugs (nonplatinum). There were 190 (65.3%) patients diagnosed with colon cancer and the rest were rectal cancer. The mean of total infusion courses was 7 (range, 4–19). Oxaliplatin was infused over 2 h; 165 (56.7%) patients received dexamethasone and antihistamine as premedication.

There were 39 patients who experienced HSRs after a few minutes from the start of the L-OHP infusion, with an overall incidence of 13.40%. The most common grade of HSRs presented was grade 2 in 15 (5.15%) patients. Grade 1 HSR was recorded in 12 (4.1%) patients, and grades 3 and 4 HSRs occurred in 9 (3.09%) and 3 (1.03%) patients, respectively. These reactions were observed after 4–15 exposures to oxaliplatin (median: 8 cycles). No patients experienced allergic reactions at his/her first oxaliplatin infusion. Patients received oxaliplatin-based regimens until disease progression or relapse, or until it was deemed intolerable due to toxicity. There were

Table 1. Clinical Characteristics of 291 Patients With Colorectal Cancer Treated With Oxaliplatin

Factors	No. Patients	Frequency
Gender		
Male	173	59.5%
Female	118	40.5%
Age		
≥60 years	173	59.5%
<60 years	118	40.5%
Site of primary disease		
Colon	190	65.3%
Rectum	101	34.7%
History of allergic drugs or food		
Yes	24	8.2%
No	267	91.8%
Oxaliplatin-free interval		
Yes	58	19.9%
No	233	80.1%
Premedication		
Yes	165	56.7%
No	126	43.3%

233 (80.1%) patients who received continuous oxaliplatin chemotherapy, whereas 58 (19.9%) patients were reexposed to oxaliplatin-based chemotherapy after an oxaliplatin-free interval; 22 patients out of 39 (56.41%) were reintroduced to oxaliplatin with premedication of dexamethasone and antihistamine.

Oxaliplatin-induced HSRs frequently occurred in seven cycles (Fig. 1). Most cases of HSRs that were observed after oxaliplatin reintroduction occurred during the second cycle of the reintroduction phase (Fig. 2). The log-rank test revealed a significant difference in the cumulative incidence of HSRs in the continuous group and uncontinuous group between the 9th and 14th cycles ($p=0.037$) (Fig. 3). Similarly, there was a significant difference in the cumulative incidence of HSRs between patients who were treated with or without premedication of dexamethasone and antihistamine ($p=0.003$) (Fig. 4).

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 (Table 2). HSRs occurred significantly less frequently in patients who received premedication with dexamethasone and antihistamine compared to those who did not ($p=0.002$). Patients who were reexposed to oxaliplatin chemotherapy have a higher incidence of HSRs than those who underwent continuous oxaliplatin chemotherapy. No other parameter (e.g., gender, age, site of primary disease, allergy to drugs or food) was significant. Multiple logistic regression analysis showed that oxaliplatin-free interval and premedication were independent variables for oxaliplatin-related HSRs ($p=0.029$ and $p=0.049$, respectively) (Table 3). In the uncontinuous group, the incidence of grades 3 and 4 HSRs (12/14, 85.71%) was significantly higher than that of grades 1 and 2 HSRs (2/14, 14.29%; $p=0.008$).

Rechallenge With Oxaliplatin

Of 39 patients, 14 (35.90%) were withdrawn from oxaliplatin administration (5, 2, and 7 patients had grades 1, 2, and 3 HSRs, respectively), 3 (7.69%) completed the full period of chemotherapy regimens, and 22 (56.41%) with HSRs resumed oxaliplatin treatment after premedication with increased doses of dexamethasone and antihistamine (Table 4). Despite premedication, 19 (86.36%) patients showed relapse of HSRs, and 3 (13.64%) did not exhibit new HSRs. Among 17 patients with grades 1 and 2 HSRs who continued oxaliplatin treatment following premedication, 3 (17.65%) fully completed oxaliplatin administration without further HSRs, 13 (76.5%) exhibited tolerance to oxaliplatin despite grades 1 and 2 HSR recurrence, and the remaining one exhibited grade 3 HSR and had to give up oxaliplatin treatment. The success rate for completing oxaliplatin administration with premedication in patients of grades 1 and 2 HSRs was 94.1%. Of

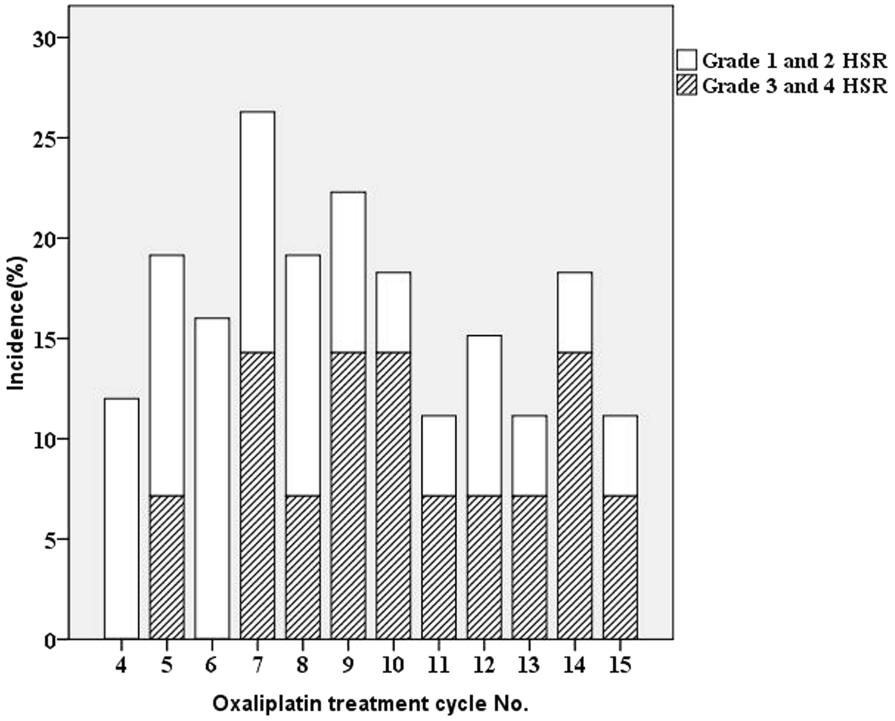

Figure 1. The number of hypersensitivity reactions (HSRs) according to the oxaliplatin treatment cycle.

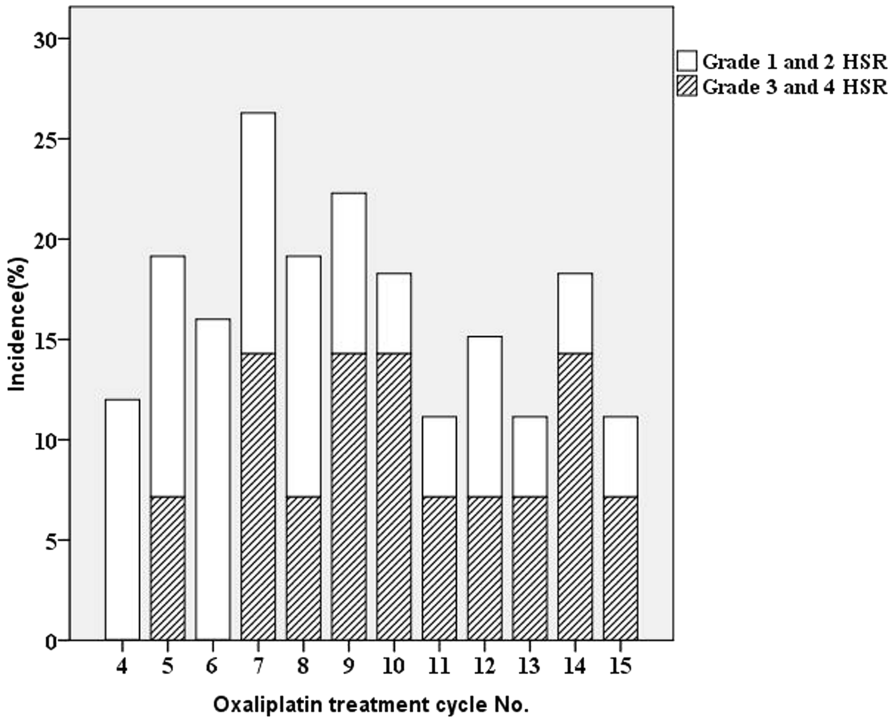

Figure 2. The number of HSRs during the reintroduction phase.

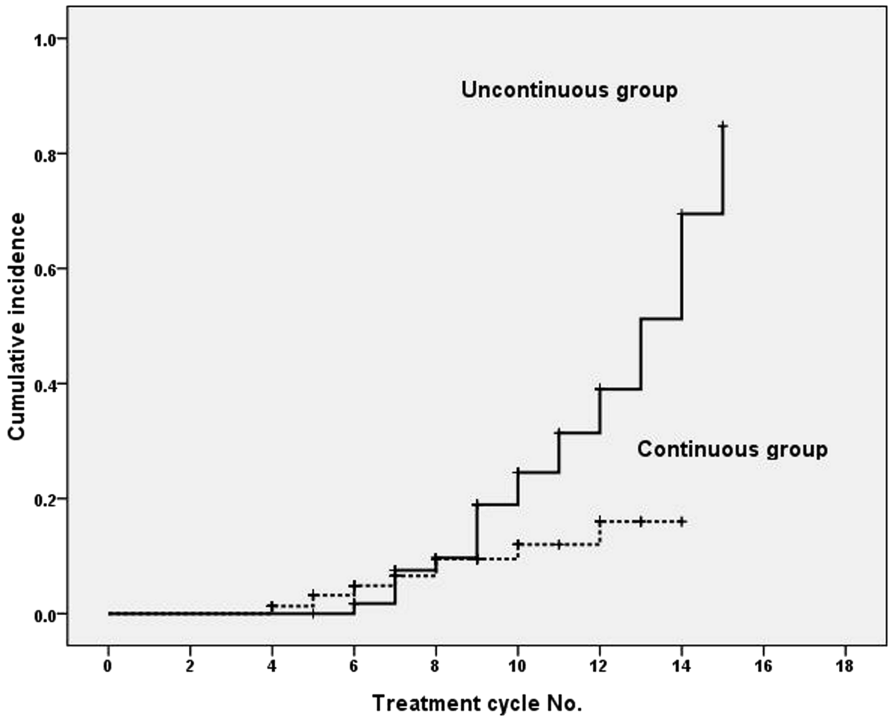

Figure 3. Cumulative incidence of HSRs according to total cycles of oxaliplatin ($p = 0.037$).

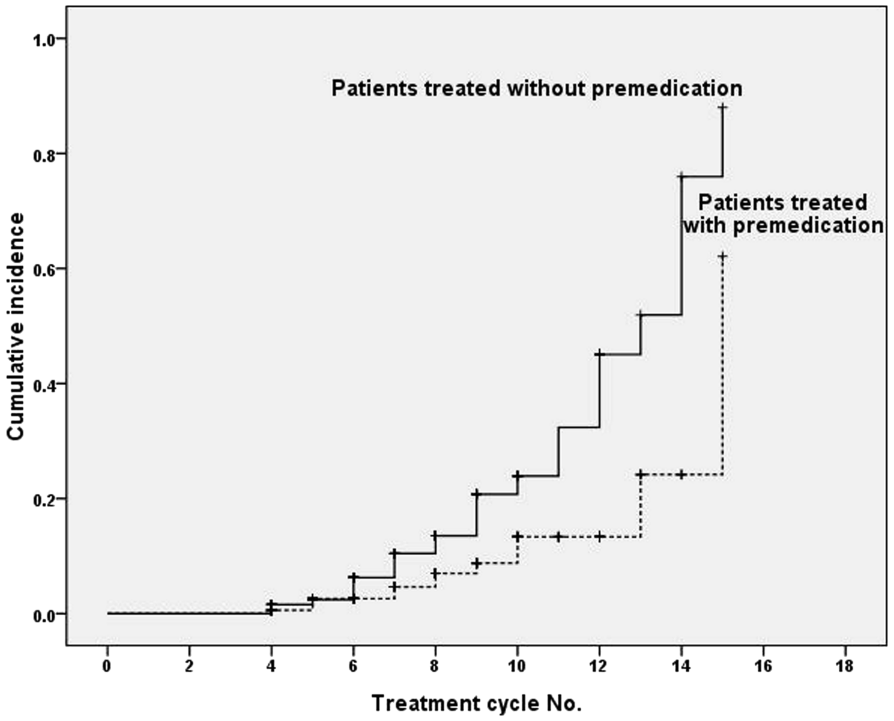

Figure 4. Cumulative incidence of HSRs according to total cycles of oxaliplatin in patients treated with or without premedication of dexamethasone and antihistamine ($p = 0.003$).

two patients with grade 3 HSRs who underwent oxaliplatin rechallenge with premedication, one experienced grade 3 HSR, and the other experienced grade 4 HSR. Although patients with grade 4 HSRs received premedication of dexamethasone, antihistamine, and slower infusion rate, anaphylaxis still occurred in these patients during their reintroduction phase. No patients with severe (grades 3 and 4) HSRs successfully completed oxaliplatin treatment with premedication.

DISCUSSION

The present retrospective study was aimed at bringing new insights to the clinical features, risk factors, and prevention of oxaliplatin-induced HSRs. Further analysis may lead to the development of effective therapeutic strategies without oxaliplatin-induced HSRs.

The prevalence of allergic reactions in the study was 13.40%, similar to the rates reported in previous articles[3,4]. Risk of HSRs usually exists after the sixth cycle of treatment[9], with an average total dose of 622.2 mg/m^2 of oxaliplatin[10]. In this study, we found that oxaliplatin HSRs frequently occur in the 7th cycle, which was similar to the results of previous studies[11,12]. Grades 1 and 2 HSRs occur mostly in the 6th cycle, whereas grades 3 and 4 HSRs occurred frequently in the 7th, 9th, and 10th cycles. The prolonged survival of patients with colorectal carcinoma increases the likelihood that the number of patients who may be reexposed to oxaliplatin could increase. Most cases of HSRs that were observed after oxaliplatin reintroduction occurred during the second cycle of the reintroduction phase[13]. Therefore, to prevent unexpected life-threatening HSRs, attention should be paid to those who were once exposed to oxaliplatin.

Table 2. Results of Univariate Analysis

Variable	No. Patients	No. HSR (%)	*p* Value
Gender			0.768
Male	173	22 (12.7)	
Female	118	17 (14.4)	
Age			0.948
≥60 years	173	23 (13.3)	
<60 years	118	16 (13.6)	
Site of primary disease			0.211
Colon	190	22 (11.6)	
Rectum	101	17 (16.8)	
Allergy to drugs or food			0.891
Yes	24	3 (12.5)	
No	267	36 (13.5)	
Oxaliplatin-free interval			0.002
Yes	58	22 (37.9)	
No	233	17 (7.3)	
Premedication			0.002
Yes	165	13 (7.9)	
No	126	26 (20.6)	

Fisher's exact test was used.

Table 3. Results of Multivariate Analysis

Variable	OR	95% CI	*p* Value
Gender			
Male/female	1.21	0.61–2.41	0.58
Age			
<60 years/≥60 years	1.07	0.54–2.12	0.84
Site of primary disease			
Colon/rectum	1.64	0.84–3.19	0.15
History of allergic to drugs or food			
Yes/no	0.66	0.20–2.21	0.50
Oxaliplatin-free interval			
Yes/no	0.41	0.19–0.91	0.029
Premedication			
Yes/no	2.02	1.02–4.01	0.045

Logistic regression analysis.

Previous studies showed that the higher incidence rate of HSRs was associated with female gender, younger age, repeated infusion, higher oxaliplatin dose, and use of oxaliplatin as salvage therapy[4,14–17]. In this study, we found that oxaliplatin-free interval and premedication with dexamethasone and antihistamine were independent risk factors. Patients who were reexposed to oxaliplatin had a higher incidence of HSRs than those who underwent consecutive oxaliplatin administration, which is consistent with the report of Mori et al.[13]. Allergic reactions with platinum compounds usually lie with the increased number of cycles during chemotherapy[18]. The median cycles of oxaliplatin administration in the continuous group and uncontinuous group were 6 and 10 cycles, respectively. Studies reported an incidence of <1% in patients who received five cycles, in contrast to an incidence of up to 27% in patients who received more than seven cycles of treatment[19]. It takes time to develop an allergy to platinum salts, as has been seen with increasing IgE antibodies over time in patients exposed to platinum salts[20]. In the uncontinuous group, the incidence of grades 3 and 4 HSRs was significantly higher than that of grades 1 and 2 HSRs. The exact cause of an increased risk of HSRs is not known.

In clinical practice, many clinicians continue to use oxaliplatin-based regimens in patients after premedication with steroids and antihistamine. One report[21] showed dexamethasone as premedication could not prevent oxaliplatin-related HSRs, whereas another report cited studies that showed the percentage of successful prevention of HSR by premedication was 37.5%–90.4% in studies of grades 1 and 2 HSRs and 42% of grades 3 and 4 HSR patients[22]. In this study, the success rate for completing oxaliplatin administration with premedication was 88.23% in grades 1 and 2 HSR patients, which suggests that premedication could be used to prevent low-grade oxaliplatin-related HSRs. At present, there is no standardized dose for premedication in cases of oxaliplatin hypersensitivity. One study reported that premedication with a high-dose steroid (dexamethasone 20 mg) significantly lowered occurrence of oxaliplatin hypersensitivity and rate of withdrawn from chemotherapy when compared to premedication with the usual dose of steroid (dexamethasone 8 mg)[23]. Therefore, an appropriate premedication steroid dose should be established for the effective management of oxaliplatin hypersensitivity. As severity of HSRs increased, the success rate by premedication decreased. There was no success in completing oxaliplatin administration with premedication in patients with severe HSRs in our study. Premedication may no longer be the preferred first option in severe HSR cases. Desensitization is reported to be an ideal strategy for maintaining the safety and effectiveness of oxaliplatin-based chemotherapy. The most widely used desensitization protocol is the classic 12-step protocol described by Castells et al.[24], in which the infusion rate is doubled every 15 min, from 2 to 80 ml/min. Lee et al.[22] reported that oxaliplatin desensitization is a safe therapy and typically has a high (80%–90%) success rate. The percentage of successful prevention of HSRs by desensitization in grades 3 and 4 HSR patients was 81.8% and 90.0%, respectively, whereas the success rate of premedication in grades 3 and 4 HSR patients was 38.5% and 11.1%. Desensitization can be applied successfully to prevent HSRs, especially in patients with severe HSRs.

In conclusion, clinicians should pay attention to patients who undergo repeated oxaliplatin infusions or reintroduction after an oxaliplatin-free interval because these patients might be at higher risk of

Table 4. Rechallenge With Oxaliplatin After First Hypersensitivity Reaction

			Outcome of Rechallenge			
Grade	*n*	Rechallenge	HSR Relieved	HSR Recurred With Tolerance	HSR Recurred Without Tolerance	Success Rate With Premedication
1	12	8	0	8	0	100%
2	15	9	3	5	1	88.9%
3	9	2	0	0	2	0
4	3	3	0	0	3	0
Total	39	22	3	13	6	72.7%

developing HSRs. In addition, our findings suggest that premedication with dexamethasone and antihistamine may decrease the risk of low-grade HSRs. Patients who develop mild to moderate HSRs can be rechallenged safely with premedication of 10 mg of dexamethasone and 10 mg of antihistamine. However, premedication was not powerful enough to prevent further HSRs for severe HSR patients during the reintroduction phase.

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