



Original Article

Characteristics and Risk Factors of Oxaliplatin-related Hypersensitivity Reactions

Yu-Yun Shao,^{1,5} Fu-Chang Hu,² Jin-Tung Liang,³ Wen-Tzu Chiu,¹ Ann-Lii Cheng,^{1,4} Chih-Hsin Yang^{1*}

Background/Purpose: Hypersensitivity reactions during oxaliplatin infusion are a major problem associated with its use. In this study, we investigated the characteristics and risk factors of these events.

Methods: All patients who had received oxaliplatin in outpatient settings from January 2006 to March 2007 in a medical center were enrolled in this retrospective study. All the oxaliplatin infusions were reviewed. Manifestations of hypersensitivity reactions and clinicopathological variables were collected from medical records.

Results: Three hundred and eighty-three patients with 3648 oxaliplatin infusions were reviewed. Forty-seven patients (12.7%) developed hypersensitivity reactions, which occurred after a median of 10 infusions. The median time of onset from start of infusion was 40 minutes. Most presentations (90.7%) were mild to moderate, but rechallenge with oxaliplatin led to a high chance of further reactions (71.4%). Cutaneous symptoms were the most prevalent manifestation, followed by respiratory symptoms. With each repeated infusion, the incidence of hypersensitivity reactions increased. Higher oxaliplatin dose per infusion was an independent risk factor for such reactions.

Conclusion: Patients treated with oxaliplatin for an extended period have a greater risk of oxaliplatin-related hypersensitivity reactions.

Key Words: chemotherapy, drug hypersensitivity, oxaliplatin

Oxaliplatin has been used extensively worldwide for treating colorectal cancer and other malignancies. However, hypersensitivity reactions to oxaliplatin are a major problem. Although the incidence rate has been found to be <2% in earlier studies,^{1,2} recent reports have shown occurrence rates as high as 10–25%.^{3–7} The risk factors remain unclear, and only one study has explored this issue by multivariate analysis.⁷

The unpredictability of hypersensitivity reactions deserves attention because they can interfere with the administration of chemotherapy and can be life-threatening.⁸ Steroids are frequently applied as premedication to prevent emesis, but they are not always effective in preventing oxaliplatin-related hypersensitivity reactions.^{9,10} The benefits of applying antihistamines and/or prolonging infusion time are also controversial.^{11,12}

©2010 Elsevier & Formosan Medical Association

Departments of ¹Oncology, ²Medical Research, ³Surgery, and ⁴Internal Medicine, National Taiwan University Hospital, Taipei, ⁵Department of Oncology, National Taiwan University Hospital Yun-Lin Branch, Yunlin, Taiwan.

Received: March 31, 2009

Revised: August 16, 2009

Accepted: August 25, 2009

***Correspondence to:** Dr Chih-Hsin Yang, Department of Oncology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 10002, Taiwan.

E-mail: chihsyang@ntu.edu.tw

In this retrospective study, we analyzed the incidence, severity, and risk factors of hypersensitivity reactions to oxaliplatin. The effects of pre-medication or prolongation of infusion time on prevention of reactions were examined.

Materials and Methods

Patients and study protocol

We searched the database of the Department of Pharmacy, National Taiwan University Hospital. All patients who had received at least one dose of oxaliplatin at an outpatient department during the period from January 2006 to March 2007 were enrolled. Medical records during oxaliplatin infusion were reviewed. Hypersensitivity reactions were classified into hypertension, fever, chills, neuropathy, and cutaneous, respiratory and digestive symptoms. The above events were excluded if they were clearly documented to be caused by conditions other than hypersensitivity reactions, such as infection or disease progression. The severity of these reactions was evaluated according to Common Terminology Criteria for Adverse Events version 3.0.¹³ In addition, data on sex, age, type of malignancy, dose of oxaliplatin administered, total number of oxaliplatin courses, premedication, and purpose of chemotherapy (adjuvant, neoadjuvant or palliative therapy) was collected. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital.

Statistical methods

Statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC, USA) and R statistical software (Free Software Foundation Inc., Boston, MA, USA). In statistical testing, two-sided p values ≤ 0.05 were considered statistically significant. The clinicopathological variables potentially associated with the development of hypersensitivity reactions to oxaliplatin were collected and subjected to univariate and multivariate analyses. These variables included: sex; age; diagnosis; pre-medication with granisetron, diphenhydramine, ranitidine or dexamethasone; and dose and infusion

time of oxaliplatin. Cox's proportional hazards model was used to estimate the effects of these potential predictors on the number of infusions or the actual time to the first hypersensitivity reaction.

The goal of regression analysis is to find parsimonious regression models that fit well with the observed data. To ensure the quality of the regression analysis results, the basic model-fitting techniques for (1) variable selection; (2) goodness-of-fit (GOF) assessment; and (3) regression diagnostics were used. Specifically, in the stepwise variable selection procedure, all the significant univariates and non-significant covariates were considered, and the significance levels for entry and for stay were set to ≥ 0.15 . The adjusted generalized R^2 and the Grønnesby–Borgan GOF test were used to assess the GOF of the fitted Cox's proportional hazards model. However, the value of the adjusted generalized R^2 for Cox's proportional hazards model is known to be low. A larger p value of the Grønnesby–Borgan GOF test indicates a better fit. The statistical tools for regression diagnostics, such as verification of proportional hazards assumption, residual analysis, detection of influential cases, and check for multicollinearity, were applied to discover model or data problems.

The Nelson–Aalen estimate of the cumulative hazard rate for the number of infusions to the first hypersensitivity reaction was plotted. The significant variables discovered in the final Cox's proportional hazards model were used for stratification. The result was further fitted by a non-parametrically smoothed curve using the locally weighted scatterplot smoothing method to check for its linearity against the number of infusions. The rationale behind this examination was that, if the occurrence of hypersensitivity reactions associated with each infusion was purely an independent event, then the smoothed curve should have been in a linear form that indicated a constant hazard rate.

Results

A total of 383 patients were enrolled in this study, and a total of 3648 oxaliplatin infusions were

Table 1. Patient characteristics (*n* = 383)*

Age (yr)	61 (21–91)
Sex, male	204 (53.3)
Total infusion courses*	8 (1–56)
Oxaliplatin interval*	
Weekly	39 (10.2)
Biweekly	281 (73.4)
Triweekly	56 (14.6)
Oxaliplatin dose (mg/m ²)†	87.8 (85.9–89.7)
Infusion time (min)†	121 (119–122)
Premedication	
Granisetron	382 (99.7)
Diphenhydramine	30 (7.8)
Ranitidine	15 (3.9)
Dexamethasone (mg)	
Nil	28 (7.3)
5	139 (36.3)
≥ 10	216 (56.4)
Type of cancer	
Colorectal cancer	335 (87.5)
Pancreatic cancer	13 (3.4)
Biliary tract cancer	7 (1.8)
Gastric cancer	20 (5.2)
Others‡	8 (2.0)
Purpose of chemotherapy§	
Total	335 (100)
Palliative	174 (51.9)
Adjuvant	126 (37.6)
Neoadjuvant	35 (10.4)

*Data presented as median (range) or *n* (%); †data presented as mean (95% confidence interval); ‡hepatocellular, nasopharyngeal, ovarian, esophageal and jejunal carcinoma; §for colorectal cancer patients. CI = confidence interval.

recorded. Their basic characteristics are listed in Table 1. Patients received a median of eight infusions, and a mean 87.8 mg/m² oxaliplatin per infusion. Oxaliplatin was given as a biweekly regimen in 73.4% of patients. About 87.5% of the patients had colorectal cancer, and about half of them received oxaliplatin for palliative therapy. Forty-seven patients had hypersensitivity reactions to oxaliplatin, for a prevalence rate of 12.3%. The first reactions developed after a median of 10 infusions of oxaliplatin (range, 2–19). Most patients (85%) had their first reactions after the sixth course (Figure 1A). The median time of onset from start of infusion was

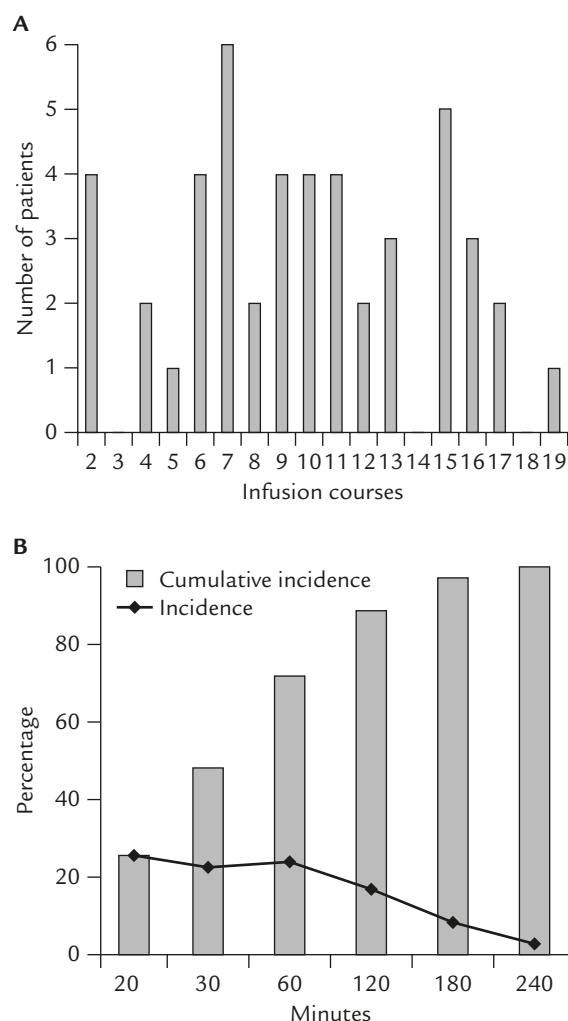


Figure 1. (A) The number of patients who developed their first hypersensitivity reaction during oxaliplatin infusion. (B) Cumulative incidence of hypersensitivity reactions from the start of oxaliplatin infusion.

40 minutes, and most reactions (88.7%) occurred within the first 2 hours (Figure 1B).

To examine the potential risk factors for development of hypersensitivity reactions, the aforementioned clinicopathological variables were put into univariate and then multivariate analyses (Tables 2 and 3). Although no variables were significant in univariate analysis, multivariate analysis by Cox's proportional hazards model revealed that oxaliplatin infusion dose and premedication with 5 mg dexamethasone were significantly associated with hypersensitivity reactions during earlier infusions. The result was very similar when analyzed with the actual time from the first infusion to the first reaction as the endpoint, although

Table 2. Univariate analysis of risk factors for hypersensitivity reaction by Cox's proportional hazards models using a hazard ratio

Variables	Earlier infusion numbers to the first HSR		Shorter time to the first HSR	
	HR	<i>p</i>	HR	<i>p</i>
Sex, male	1.425	0.230	1.171	0.590
Age	1.004	0.750	1.015	0.215
Diagnosis (<i>vs.</i> CRC)				
Pancreatic cancer	4.252	0.052	1.362	0.669
Biliary tract cancer	2.276	0.418	1.302	0.794
Gastric cancer	0.440	0.417	0.380	0.338
Oxaliplatin dose	1.007	0.154	1.005	0.292
Infusion time	0.995	0.652	0.989	0.285
Premedication				
Granisetron	20.17	0.926	20.18	0.813
Diphenhydramine	1.623	0.270	1.968	0.122
Ranitidine	2.669	0.104	3.921	0.177
Dexamethasone	3.492	0.216	2.192	0.192

HR = Hazard ratio; CRC = colorectal cancer; HSR = hypersensitivity reaction.

Table 3. Multivariate analysis of risk factors for hypersensitivity reaction by Cox's proportional hazards models using a hazard ratio

Covariate	Parameter estimate	Standard error	Wald's χ^2 test	<i>p</i>	HR (95% CI)
1. Earlier infusion numbers to the first hypersensitivity reaction					
Premedication with 5 mg dexamethasone	0.739	0.310	5.691	0.017	2.094 (1.141–3.843)
Oxaliplatin dose	0.023	0.008	8.210	0.004	1.024 (1.007–1.040)
2. Shorter time to the first hypersensitivity reaction					
Premedication with 5 mg dexamethasone	0.558	0.298	3.495	0.062	1.747 (0.973–3.135)
Oxaliplatin dose	0.013	0.008	2.758	0.097	1.013 (0.998–1.028)

HR = Hazard ratios; CI = confidence interval.

the two factors became only of borderline significance. Only 7% of patients did not receive steroids as premedication (Table 1), therefore, the result with 5 mg dexamethasone as a risk factor mainly reflected its comparison with ≥ 10 mg dexamethasone.

Stratified by the two significant variables among the whole patient group, the Nelson–Aalen estimator plot demonstrated the cumulative hazards during each infusion (Figure 2). The locally weighted scatterplot smoothing method was used to fit the

curves to facilitate judgment of linearity. The plots were clearly not simply linear. This demonstrated that oxaliplatin-related hypersensitivity reactions did have an increased incidence with each repeated infusion.

Eighty-six episodes of hypersensitivity reactions were recorded. During the first reactions, cutaneous symptoms were the most prevalent manifestation (70.9%, Table 4), followed by respiratory symptoms (30.3%) and fever (25.5%).

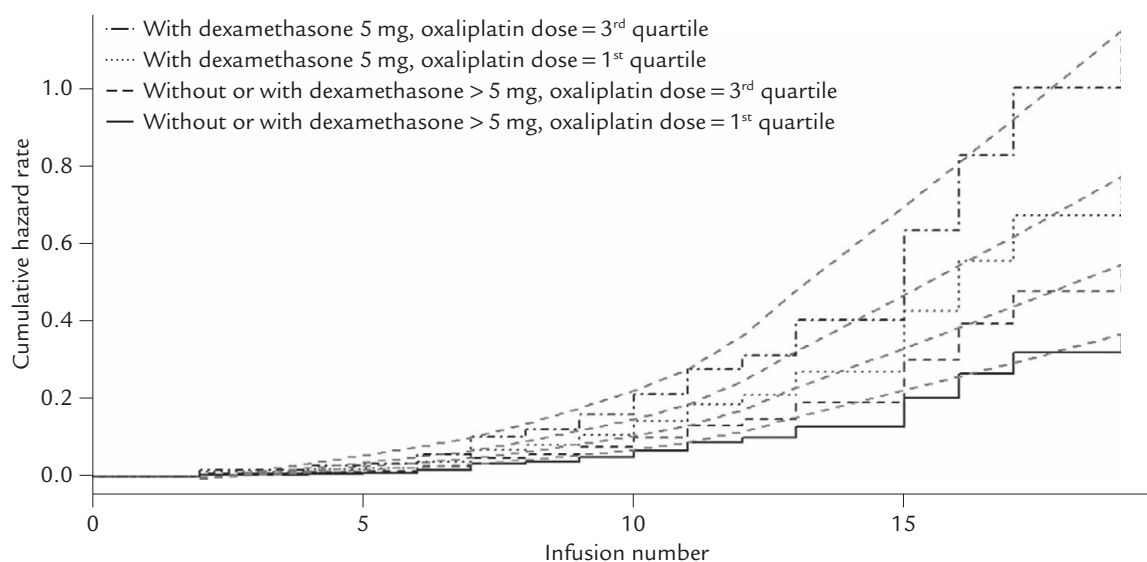


Figure 2. Nelson–Aalen estimates of cumulative hazard rates for the number of infusions to the development of the first hypersensitivity reaction, stratified by the two statistically significant risk factors. The first and third quartiles of oxaliplatin doses per body surface area were chosen for illustrative purposes. The smoothed curves (the smoothed dashed lines) were plotted by using the locally weighted scatterplot smoothing method in the free *R* software, which uses locally-weighted polynomial regression with smooth span (f) = 2/3 to check for its linearity against the number of infusions.

Table 4. Manifestations of the hypersensitivity reactions ($n = 47$)

Symptom	
Cutaneous	61 (70.9)
Respiratory symptoms	26 (30.3)
Fever	22 (25.5)
Hypertension	16 (18.6)
Chills	16 (18.6)
Peripheral neuropathy	12 (14.0)
Digestive symptoms	17 (19.8)
Consciousness change	3 (3.5)
Grade	
1–2	78 (90.7)
3–5	8 (9.3)
Onset (min)	40 (5–215)

*Data presented as n (%) or median (range).

Most of the reactions were mild. Over ninety percent were grade 1 or 2 reactions. Nonetheless, one patient died of anaphylactic shock during his fourth oxaliplatin infusion. There had been no discomfort during the previous three infusions. A review of the other seven events with grade 3/4 toxicity showed that only three were preceded by prior mild episodes.

After hypersensitivity reactions, 35 patients received rechallenge with a mean 4.5 infusions. Twenty-five of these (71.4%) developed subsequent events. Three patients had oxaliplatin infusion prolonged to 4 hours, but all developed hypersensitivity reactions. The manifestations and severity of these reactions were generally similar to the first episodes.

Discussion

We here present a retrospective study on oxaliplatin-related hypersensitivity reactions. The occurrence rate of hypersensitivity reactions was 12.3% and they developed after a median of 10 courses. These results were consistent with previous studies.^{3–7,10} The onset after the start of infusion varied, ranging from within 15 minutes to 20 hours later.^{4,14} In our study, about 90% of patients had symptoms within the first 2 hours. Oxaliplatin was mostly applied in a 2-hour infusion, which implied that most reactions occurred during infusion.

Several limitations of this study should be noted. Hypersensitivity symptoms were not actively

pursued, therefore, mild discomforts and delayed reactions after departure from hospital might have been ignored or forgotten. Frail or completely bedridden patients who never received chemotherapy in an outpatient setting were not enrolled. Therefore, the incidence of hypersensitivity reactions in this study was likely to have been underestimated. Besides, the application interval of oxaliplatin was diverse. However, multivariate analyses demonstrated similar results regardless of whether the endpoints were infusion numbers or actual time from start of infusion.

Hypersensitivity reactions related to oxaliplatin, unlike taxanes, usually developed after repeated exposure. However, this observation could have been merely a presentation of cumulative incidence of independent events because more exposure might have led to a greater risk of reaction. By plotting cumulative hazards, we actually demonstrated that repeated infusions did indeed result in a higher risk of reaction. Other platinum compounds, such as cisplatin, also cause similar reactions after repeated exposure.^{15,16} One of the first described hypersensitivity reactions occurred in a 15-year-old boy during the eighth infusion.¹⁷ Likewise, the highest incidence of hypersensitivity to carboplatin occurred at approximately the eighth cycle.¹⁸ These findings indicate that hypersensitivity to platinum complexes is prone to develop after multiple uncomplicated courses.

Other than repeated infusion as a risk factor, we found that higher infusion doses were associated with earlier reactions, which has not been reported before. The other significant risk factor was the premedication with 5 mg dexamethasone. Very few patients did not receive steroids; therefore, this result mainly compared 5 mg with ≥ 10 mg dexamethasone. However, when we compared patients with 5 mg and ≥ 10 mg dexamethasone only, the result became non-significant. Therefore, whether higher doses of steroid do have a protective effect remains to be elucidated.

A previous study that explored risk factors for oxaliplatin-related hypersensitivity reactions found younger age, female sex, and salvage therapy to be predictors for reactions.⁷ These variables

were not significant in our study. One reason is the ethnic differences between the participants in this study and the other study, and the other possibility is that the two predictors, the doses of oxaliplatin and dexamethasone, in our study were not analyzed in the earlier study.

Thirty-four of our patients elected to receive oxaliplatin again after prior hypersensitivity reactions. The occurrence rate of adverse reactions surged to 71.4%, which was much higher than the previously reported 29–50%.^{4,10,12} Prior studies had limited patient numbers and fewer rechallenges, but our patients received 4.5 additional infusions on average. The increased exposure could explain the high rate of occurrence of hypersensitivity. Some desensitization protocols have had success with expanding the infusion time to 24 hours.^{19–23} Three of our patients had 4-hour infusions during rechallenge, but all three failed rechallenge and developed hypersensitivity reactions.

In conclusion, repeated oxaliplatin infusion actually increased the chances of oxaliplatin-related hypersensitivity reactions. Rechallenge could lead to a high prevalence of further episodes.

References

1. de Gramont A, Vignoud J, Tournigand C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *Eur J Cancer* 1997;33:214–9.
2. Thomas RR, Quinn MG, Schuler B, et al. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003;97:2301–7.
3. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343–51.
4. Brandi G, Pantaleo MA, Galli C, et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003;89:477–81.
5. Gowda A, Goel R, Berdzik J, et al. Hypersensitivity reactions to oxaliplatin: incidence and management. *Oncology (Williston Park)* 2004;18:1671–84.
6. Kim BH, Bradley T, Tai J, et al. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology* 2009;76:231–8.
7. Polyzos A, Tsavaris N, Gogas H, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology* 2009;76:36–41.

8. Shao YY, Hong RL. Fatal thrombocytopenia after oxaliplatin-based chemotherapy. *Anticancer Res* 2008;28:3115–7.
9. Stahl M, Koster W, Wilke H. Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001;12:874.
10. Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol* 2006;17:259–61.
11. Lenz G, Hacker UT, Kern W, et al. Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer Drugs* 2003;14:731–3.
12. Lee MY, Yang MH, Liu JH, et al. Severe anaphylactic reactions in patients receiving oxaliplatin therapy: a rare but potentially fatal complication. *Support Care Cancer* 2007;15:89–93.
13. National Cancer Institute U.S.: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [Date accessed: Mar 1, 2009]
14. de Vries RS, Mattijssen EJ, van Sorge AA. Serious delayed hypersensitivity reaction to oxaliplatin. *Ann Oncol* 2006;17:1723–4.
15. Saunders MP, Denton CP, O'Brien ME, et al. Hypersensitivity reactions to cisplatin and carboplatin—a report on six cases. *Ann Oncol* 1992;3:574–6.
16. Onoyama Y, Umezu T, Kuriaki Y, et al. Hypersensitivity reactions to cisplatin following multiple uncomplicated courses: a report on two cases. *J Obstet Gynaecol Res* 1997;23:347–52.
17. Khan A, Hill JM, Grater W, et al. Atopic hypersensitivity to cis-dichlorodiammineplatinum(II) and other platinum complexes. *Cancer Res* 1975;35:2766–70.
18. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer* 2005;15:13–8.
19. 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;20:1146–7.
20. Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004;9:546–9.
21. 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;15:605–7.
22. Mis L, Fernando NH, Hurwitz HI, et al. Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005;39:966–9.
23. Edmondson DA, Gruling BJ, Urmanski AM, et al. Oxaliplatin hypersensitivity: case report and successful repeat desensitization. *Am J Ther* 2007;14:116–8.