

Oxaliplatin Hypersensitivity: Evaluation, Implications of Skin Testing, and Desensitization

Johnson T. Wong, MD, Morris Ling, MD, Sarita Patil, MD, Aleena Banerji, MD, and Aidan Long, MD *Boston, Mass*

What is already known about this topic? Hypersensitivity reactions to platin agents, including oxaliplatin, are common, and desensitizations may be performed.

What does this article add to our knowledge? Retrospective review of 48 patients with oxaliplatin hypersensitivity highlights similarities and differences of patients with carboplatin/cisplatin hypersensitivity, prognostic significance of skin testing, and criteria for choice of desensitization protocols.

How does this study impact current management guidelines? Skin testing, history, and reactions during previous desensitizations are helpful in determining the choice of 3 protocols. Drug-induced thrombocytopenia and hemolytic anemia may develop. Nearly all patients can be desensitized successfully.

BACKGROUND: Oxaliplatin hypersensitivity (OXS) presents a challenge in the treatment of oxaliplatin-sensitive malignancies. **OBJECTIVE:** To analyze patient characteristics of patients with OXS, skin test results, and desensitization outcomes to optimize management.

METHODS: Over 5 years, 48 patients with OXS were referred to the allergy/immunology unit at Massachusetts General Hospital. Their clinical reaction patterns were analyzed. Immediate hypersensitivity skin testing was used for risk stratification, and drug desensitizations were performed by using 3 related continuous intravenous protocols that were chosen based on clinical history, skin test reactivity, and the patients' previous desensitization outcomes.

RESULTS: OXS occurred in both sexes, with mostly gastrointestinal-related tumors. Hypersensitivity reaction (HSR) onset had occurred during any course of therapy (course nos. 1-28), with a median onset at course no. 8. HSR to oxaliplatin was similar to those observed with cisplatin and carboplatin, including cutaneous, cardiovascular, pulmonary, and gastrointestinal symptoms. However, neurologic symptoms, including tingling, and systemic symptoms, including fever and chills, occurred more often in patients with OXS. Unique to OXS, 2 patients developed drug-induced thrombocytopenia; 1 patient also developed drug-induced hemolytic anemia. Skin

testing was positive for the majority of patients with OXS (27/46 [59%]) and correlated with a greater likelihood of developing an HSR during subsequent desensitizations. We safely performed 200 desensitizations in 48 patients with OXS.

CONCLUSION: OXS is common with much similarity to other platin agents but also have distinct differences in the onset of hypersensitivity, sex, tumor type, drug-induced hemolytic anemia, and drug-induced thrombocytopenia. Skin testing was helpful for risk stratification. All of the desensitizations were completed successfully. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:40-5)

Key words: Oxaliplatin; Carboplatin; Cisplatin; Hypersensitivity; Onset; Skin test; Continuous; Intravenous; Desensitization

Platinum drugs are antineoplastic compounds that are used for treating a variety of cancers.¹ The 3 principal agents currently used for chemotherapy are cisplatin, carboplatin, and oxaliplatin. Oxaliplatin is a third-generation platinum derivative primarily used for treating various gastrointestinal (GI) malignancies, particularly colorectal cancer,^{2,3} whereas cisplatin and carboplatin are used for treating ovarian, lung, and other cancers.⁴⁻⁶ Hypersensitivity reactions (HSR) to oxaliplatin are common, with a reported incidence of 7% to 24% in several case series and 1 literature review.⁷⁻¹⁸ Several groups, including our institutions, have pioneered desensitization protocols that permit the safe administration of these agents that otherwise would have been denied to patients with oxaliplatin hypersensitivity (OXS).¹⁹⁻²³ In this study, we examined the HSR patterns, skin testing results, and management outcomes of patients with OXS. This was compared with our experience of patients with carboplatin hypersensitivity (CAS) and/or cisplatin hypersensitivity (CIS).

METHODS

Patients

The data of patients with OXS referred to the allergy/immunology unit at Massachusetts General Hospital from July

Department of Medicine, Allergy and Immunology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Mass

No funding was received for this work.

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

Received for publication June 12, 2013; revised July 23, 2013; accepted for publication August 6, 2013.

Available online November 4, 2013.

Corresponding author: Johnson T. Wong, MD, Medicine, Cox 2, Massachusetts General Hospital, Boston, MA 02114. E-mail: jwong1@partners.org. 2213-2198/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2013.08.011>

Abbreviations used

CAS- Carboplatin hypersensitivity
CIS- Cisplatin hypersensitivity
DIHA- Drug-induced hemolytic anemia
DITP- Drug-induced thrombocytopenia
GI- Gastrointestinal
HRP- High-risk protocol
HSR- Hypersensitivity reaction
Ig- Immunoglobulin
IP- Intermediate protocol
OXS- Oxaliplatin hypersensitivity
RP- Rapid protocol

2007 to June 2012 were retrospectively reviewed with regard to demographic, hypersensitivity pattern, time of onset of the hypersensitivity, skin test result, and desensitization outcome. Institutional review board approval was obtained for this study.

Skin testing

All the patients who had OXS were encouraged to have immediate hypersensitivity skin testing whenever possible after the initial HSR. Skin prick testing was performed with oxaliplatin 0.5 mg/mL with appropriate histamine and saline solution controls. Intradermal testing was performed with oxaliplatin at 0.05 mg/mL, 0.5 mg/mL, and up to 5 mg/mL if the skin test was negative at the lower concentrations.^{19,24} A positive skin test to oxaliplatin was defined as a wheal of diameter 3 mm greater than that seen with a saline solution negative control. Repeated skin testing was performed in most cases in which the initial skin test was negative to determine the rate of conversion. Repeated skin test was performed in a few patients in whom the initial skin test was positive either 3 to 5 weeks after the first testing or after a relapse that required additional courses of oxaliplatin.

Desensitization protocols

All patients with OXS underwent desensitization with 1 of 3 closely related continuous intravenous desensitization protocols that varied in starting concentration, the number of steps (8-13), and the total time taken was 4.7-16 hours (Table I). These protocols were adopted standardized protocols for Partners Institutions (Massachusetts General Hospital, Brigham and Women's Hospital, and Dana Farber Cancer Institute). They were similar to our published protocols used for CAS and CIS,^{20,23} which were modifications of our previously published vancomycin desensitization protocol.²⁵ The particular protocol chosen for each desensitization was dependent on the patients' HSR history, skin test result, date from last reaction, and HSR pattern during the last desensitization. Patients with a negative skin test generally underwent the rapid protocol unless their reactions were within 1 month of skin testing. Patients with a negative skin test whose HSRs occurred within 1 month were started on the intermediate protocol due to the possibility of a false-negative skin test. Patients with a positive skin test were started on the intermediate protocol. Modifications were made by inserting intermediate steps for selected patients with persistent reaction during a certain step in their desensitization. Patients who continued to develop reactions during the previous desensitization despite modifications to the intermediate protocol were placed on the high-risk desensitization protocol.

RESULTS

Patient characteristics and tumor types

Forty-eight patients with OXS were referred to the allergy/immunology unit and underwent 200 desensitizations during the 5-year period. In the past few years, the number of referred patients with OXS was approximately 60% to 75% of the number of referred patients with CAS (dominant) and CIS (minor). The demographics of the patients with OXS are depicted in Table II. Eighteen of the patients were men (38%), and 30 were women (62%). The average age at the time of consultation was 58 years (range, 22-79 years). Most tumors were GI in origin (n = 45 [94%]), with a few metastatic adenocarcinoma of unknown origin (n = 3 [6%]). Cecal, colonic, and rectal-sigmoidal carcinoma (n = 32 [67%]) made up two-thirds of the tumors, with esophageal, gastric, and duodenal carcinoma, which comprised another significant subgroup (n = 6 [13%]). Pancreatic cancer (n = 5 [10%]), cholangiocarcinoma (n = 1 [2%]), and goblet cell cancer (n = 1 [2%]) made up the remaining GI tumors.

HSRs

HSRs on presentation are summarized in Table III. The most common HSRs were cutaneous, including flushing, urticaria, and palmar erythema (78%). Cardiovascular reactions, especially hypertension and hypotension (33%); pulmonary reactions, including shortness of breath, chest tightness, and cough (35%); and GI reactions, including nausea, vomiting, and diarrhea (29%) were the next major groups of reactions. Oropharyngeal symptoms, including throat tightness, globus, and hoarseness (19%); systemic symptoms, including chills and/or rigor and fever (19%); neurologic reactions, including tingling, dizziness, and jitteriness (13%); drug-induced immune-mediated thrombocytopenia (DITP); and musculoskeletal symptoms, including back pain and spasms (6%) made up the remainder of the HSRs.

Course number of the first HSR

The course number of the onset of HSRs are depicted in Figure 1. The first HSRs may occur during any time, from the first course to the 28th course, with no marked modal clustering, although slightly more occurred during the 5th and 10th courses. The median course number of onset was the 8th course.

Skin test results and desensitization outcomes

The skin test results and desensitization outcomes are depicted in Table IV. Forty-six of the 48 patients were skin tested with oxaliplatin. Two patients were unable to be tested. Of the 46 patients who underwent skin testing, 25 (54%) were positive on the first testing. Of these 25 patients with an initially positive skin test, the majority were not retested. Six of these patients were retested either 3 to 5 weeks after the first testing or after a relapse that required additional courses of oxaliplatin. Upon retesting, 3 of the 6 patients converted to negative. Of the 22 initially skin test positive who did not convert to negative, 10 patients (45%) developed HSR during one or more desensitizations. Among this group, HSR occurred during 28 of the 120 desensitizations (23%). Two of the 3 who converted from a positive skin test to a negative skin test developed HSR during at least one of the desensitizations. These 3 patients developed HSR in 6 of the 24 desensitizations (25%). Twenty-one patients initially had a negative skin test (46%). Nineteen of these

TABLE I. Desensitization protocols for the 125-mg dose*†

Step no.	Time (h:min)	RP		IP		HRP	
		Concentration (mg/mL)	Infusion rate (mL/h)	Concentration (mg/mL)	Infusion rate (mL/h)	Concentration (mg/mL)	Infusion rate (mL/h)
1	0:00	0.05	5	0.005	2.5	0.000125	20
2	0:15	0.05	10	0.005	5	0.000125	40
3	0:30	0.05	20	0.005	10	0.000125	80
4	0:45	0.05	40	0.005	20	0.00125	20
5	1:00	0.5	10	0.05	5	0.00125	40
6	1:15	0.5	20	0.05	10	0.00125	80
7	1:30	0.5	40	0.05	20	0.0125	20
8 RP‡	1:45-4:40	0.5	80				
8 IP and HRP§	1:45			0.05	40	0.0125	40
9	2:00			0.5	10	0.0125	80
10	2:15			0.5	20	0.125	20
11	2:30			0.5	40	0.125	40
12	2:45			0.5	60	0.125	60
13 IP	3:00-5:45			0.5	80		
13 HRP¶	3:00-15:08					0.125	80

RP, Rapid protocol; IP, intermediate protocol; HRP, high-risk protocol.

*Adopted standardized protocol for Partners Institutions (Massachusetts General Hospital, Brigham and Women's Hospital, Dana Farber Cancer Institute). Total amount of drug was diluted into 250 mL of diluent for RP and IP, 1000 mL of diluent for HRP as the final concentration. Serial 10-fold dilutions was made for RP (1 dilution), IP (2 dilutions), and HRP (3 dilutions); hence the concentration of each drug varies for the total dose of drug.

†Previous Massachusetts General Hospital protocols used a fixed final drug concentration for each protocol: oxaliplatin (0.5 mg/mL), carboplatin (1 mg/mL), cisplatin (1 mg/mL) with serial 10-fold^{20,23} dilutions used for starting concentrations.

‡Duration of step no. 8 for RP.

§Duration of step no. 8 for IP and HRP.

||Duration of step no. 13 for IP.

¶Duration of step no. 13 for HRP.

TABLE II. Patient demographics and tumor types (N = 48)

Sex, no. (%)	
Men	18 (38)
Women	30 (62)
Age (y) at onset of allergy/immunology consultation, mean (range)	
58 (22-79)	
Tumor type, no. (%)	
Esophageal	2 (4)
Gastric	3 (6)
Duodenal	1 (2)
Cecal	1 (2)
Colonic	18 (38)
Sigmoid/rectal	13 (27)
Metastatic adenocarcinoma of unknown origin	3 (6)
Cholangiocarcinoma	1 (2)
Goblet cell	1 (2)
Pancreatic	5 (10)

patients with an initially negative skin test underwent additional testing (2-4 total skin tests each for these patients). Seventeen of these 19 patients remained skin test negative (89%). Of the 19 patients who were initially skin test negative and who did not convert to positive (17 negative on repeated skin tests and 2 without repeated skin tests), 4 (21%) developed a HSR during one or more of the desensitizations. Among this group, HSR occurred during 5 of the 42 desensitizations (12%). Of the 2 patients who converted to a positive skin test, the time between their original reactions and the skin test was 16 days and 18

TABLE III. HSRs (N = 48)

Reactions	Patients, no. (%)
Oropharynx (throat tightness, tongue swelling, hoarseness)	9 (19)
Cardiovascular (tachycardia/bradycardia, blood pressure alterations, chest pain dizzy/lightheaded)	16 (33)
Pulmonary (chest tightness, shortness of breath, cough, nasal)	17 (35)
GI (nausea/vomiting/diarrhea, abdominal pain)	14 (29)
Musculoskeletal (arthralgia, spasm, pain)	3 (6)
Cutaneous (erythema/flushing, pruritus, urticaria, palmar)	38 (78)
Delayed cutaneous (rash, erythema/flushing, pruritus)	1 (2)
Neurologic (tingling, dizzy, tunnel vision jittery, seizure, difficulty focusing)*	6 (13)
Systemic (fever, chills/rigors, somnolence)	9 (19)
Drug-induced immune-mediated thrombocytopenia	1 (6)

*One patient had tunnel vision jittery, seizure, difficulty focusing, and tingling.

months, respectively. One of these 2 patients developed an HSR during 1 of 12 desensitizations (8%). Both the percentage of patients (45% vs 21%) and the frequency of infusions (23% vs 12%) that developed HSR were significantly higher for patients with initially positive skin test compared with patients with a negative skin test by the single-tail Student *t* test, *P* = .05 and .04, respectively. Although significant HSRs complicated a significant number of desensitizations, all 200 desensitizations were able to be completed safely.

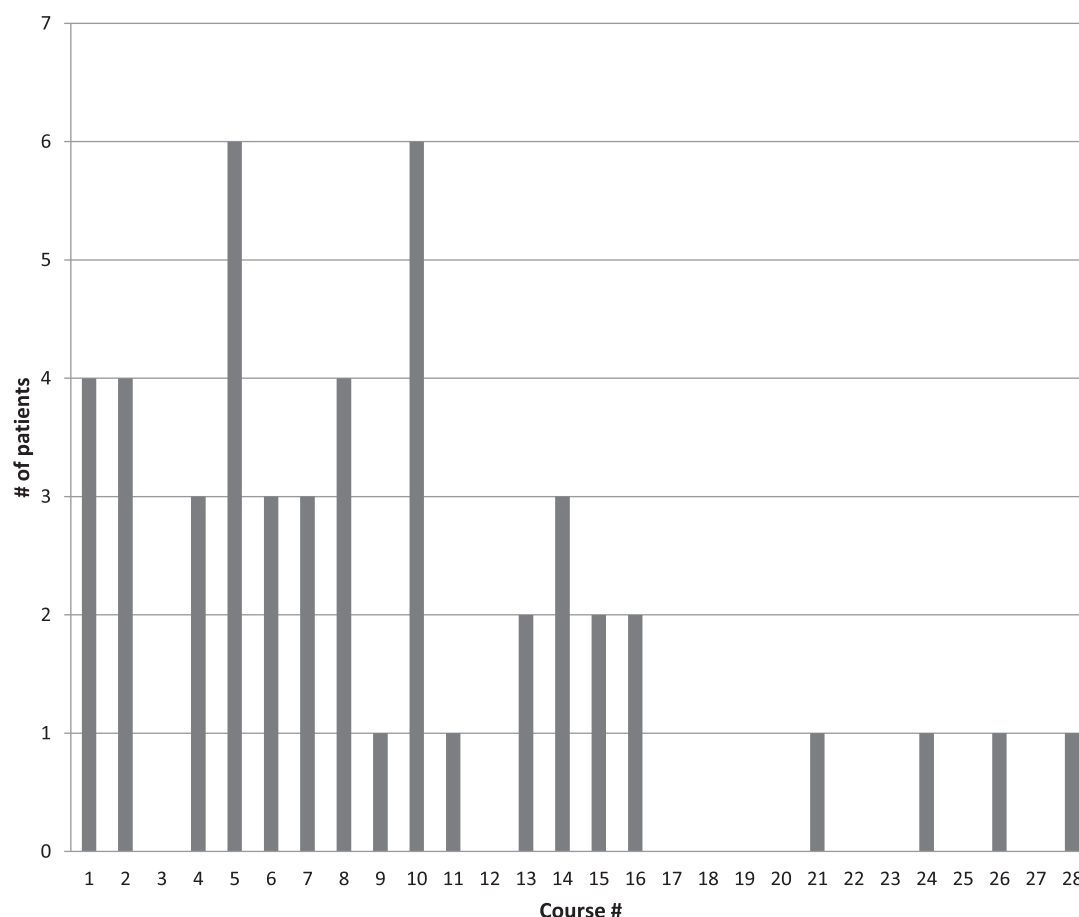


FIGURE 1. The course number of the first HSR. The number of patients who developed their first OXS was plotted on the y-axis versus the course number on the x-axis.

TABLE IV. Skin test results and desensitization outcome

Skin test status	No. of patients	Patients with reaction, no. (%)	No. desensitization	Desensitization with reactions, no. (%)
Positive	22	10 (45)*	120	28 (23)†
Positive converted to negative	3	2 (67)	24	6 (25)
Negative remain negative	19	4 (21)*	42	5 (12)†
Negative converted to positive	2	1 (50)	12	1 (8)

* $P = .05$ by a single-tail Student t test.

† $P = .04$ by a single-tail Student t test.

HSRs during desensitization

The HSRs that occurred during desensitization are shown in Table V. The reactions were largely similar to the original HSR. One patient with DITP at the time of initial consultation continued to have DITP, and 1 patient developed DIHA and DITP during desensitization.

DISCUSSION

Oxaliplatin is an important chemotherapeutic agent for treating various GI tumors, as is reflected in our patient populations. Hypersensitivity to oxaliplatin is common and is the second most frequent reason for chemotherapy-related consultations to the allergy/immunology unit at Massachusetts General Hospital, second only to carboplatin. Unlike carboplatin and

cisplatin, which are predominantly used to treat female patients with ovarian and breast carcinomas, nearly 40% of the patients with OXS were men. The pattern of initial HSR was similar to that seen in our patients with CAS and CIS, with mainly cutaneous involvement, cardiovascular, pulmonary, and GI reactions. The presence of palmar erythema, a notable feature of CAS and CIS, was also seen with OXS. In comparison with CAS and CIS, there was a greater incidence of neurologic symptoms, particularly tingling, which may reflect the high neurotoxicity of oxaliplatin.^{26,27} There also was a higher incidence of systemic symptoms, such as chills and/or rigor and fever. The time and course number of the initial development of HSR was substantially different for OXS when compared with CAS and CIS. Although the median onset of course no. 8 for OXS was similar to the median for CAS and CIS, the distribution was very

TABLE V. Reaction patterns during desensitizations (N = 18)

Reactions	Patients, no. (%)
Oropharynx (throat tightness)	1 (6)
Cardiovascular (tachycardia/bradycardia, blood pressure alterations, atrial fibrillation)	5 (28)
Pulmonary (chest tightness, shortness of breath, cough)	5 (28)
GI (nausea/vomiting/diarrhea)	2 (11)
Musculoskeletal (back pain)	2 (11)
Cutaneous (erythema/flushing, pruritus, urticaria, palmar)	10 (56)
Neurologic (tingling, headache)	3 (17)
Systemic (fever, chills and/or rigors)	5 (28)
Immune mediated hemolytic anemia*	2 (11)
Immune mediated thrombocytopenia*	1 (6)

*Not seen in patients with CAS and CIS.

different. Unlike the dominance of HSR onset clustering around course nos. 8 and 9, with a second peak at course nos. 13 and 14 that had been consistently observed in CAS and CIS, there was no significant clustering observed in OXS. There was a nearly equal number that occurred during course nos. 1 to 5 ($n = 17$ [35%]), course nos. 6 to 10 ($n = 17$ [35%]) versus later courses ≥ 11 ($n = 14$ [29%]), although there might be slight peaks around course nos. 5, 10, and 14. Clustering around the 8th and 9th courses with a second peak at the 13th and 14th courses for CAS and CIS coincided with the second and third reexposures after a prolonged period of abstinence for carboplatin and cisplatin (generally administered in multiples of 6 courses), with the first reexposure likely generating a recall reaction for the second and third reexposure. This does not appear to be the case for OXS because a significant number occurred during the first and second lifetime exposure (17%), which suggests that a prolonged period of exposure is not necessary for some of the patients. Some patients, however, did require >10 courses of exposure (29%) before experiencing OXS. Some of the differences may be due to the patterns of administration of oxaliplatin, which is generally given every 2 to 3 weeks continuously until remission. However, there appeared to be fundamental differences given that HSR may occur with the first lifetime exposure, which suggests that oxaliplatin is capable of more rapid sensitization than carboplatin and cisplatin. Skin testing for OXS was instructive and positive at some point for 27 patients (59%) (25 with positive skin test on the first testing and 2 converted on subsequent skin testing). Of the 21 patients with a negative skin test, 20 underwent repeated skin testing, with 18 remaining with a negative skin test. Skin test status does have predictive value in determining the rate of desensitization and the likelihood of developing an HSR during desensitization. Patients with OXS and a positive skin test were approximately twice as likely (45% of patients and 23% of desensitizations) as patients with a negative skin test (21% of patients and 12% of desensitization) ($P = .05$ and $.04$, respectively; single-tailed Student t test) to develop a reaction during desensitization, despite the former starting with a slower protocol. The number of patients who converted their skin test status was too small to be analyzed separately, although the outcomes of these patients appeared to be largely congruent with their initial skin test result. The HSRs that developed during the desensitizations largely recapitulated their initial reactions but were generally milder. Unlike CAS and CIS, the

development of DIHA and DITP in a small subgroup of patients appeared to be unique to OXS among platinum agents, which generally developed after multiple courses of treatment. One patient who developed DIHA and DITP during her desensitizations underwent additional desensitizations because there was no alternative effective oncologic agent. One patient who had DITP before the desensitization received one course of desensitization but then stopped because an alternative oncologic treatment was devised. The details of their clinical course will be the subject of a separate report. A negative initial skin test, although predictive of a lower likelihood of developing a HSR during desensitization, does not preclude a severe HSR from occurring. The one patient who developed anaphylaxis severe enough to require epinephrine during desensitization repeatedly had negative skin tests. Patients with positive skin tests likely have an IgE-mediated mechanism as a major or significant contributing mechanism. Those with repeatedly negative skin tests may represent a mixture of patients whose reactions occur via a non-IgE mediated pathway, those whose IgE level was too low to be detected by skin testing, or whose platinum-specific IgE may be directed against a metabolite or a bound agent.

In summary, OXS is common. The hypersensitivity patterns are similar to other platinum agents although there were increased neurologic and systemic reactions. Immune-mediated hemolytic anemia and immune-mediated thrombocytopenia appeared to be unique among platinum agents. The onset of HSR may occur at any given course, unlike the clustering observed with other platinum agents. Skin testing does have prognostic significance and provides guidance in choosing the appropriate rate of desensitization and indicates a higher probability of HSR during subsequent desensitization. Although some patients developed significant HSR during desensitization, nearly all desensitizations allowed the full dose of oxaliplatin to be administered to treat their cancer.

Acknowledgments

We thank Kristjana Toli for help gathering the patient information and all the Massachusetts General Hospital fellows who performed the patient evaluations, skin testings, desensitizations, and keeping the patient log.

REFERENCES

- Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer* 2007;7:573-84.
- de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938-47.
- Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.
- Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999;17:409-22.
- Colombo N, Guthrie D, Chiari S, Parmar M, Qian W, Swart AM, et al. International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer Inst* 2003;95:125-32.
- Trimbos JB, Parmar M, Vergote I, Guthrie D, Bolis G, Colombo N, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant Chemotherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95:105-12.
- Mori Y, Nishimura T, Kitano T, Yoshimura K, Matsumoto S, Kanai M, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology* 2010;79:136-43.
- Shibata Y, Ariyama H, Baba E, Takii Y, Esaki T, Mitsugi K, et al. Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan. *Int J Clin Oncol* 2009;14:397-401.

9. Yanai T, Iwasa S, Hashimoto H, Kato K, Hamaguchi T, Yamada Y, et al. Successful rechallenge for oxaliplatin hypersensitivity reactions in patients with metastatic colorectal cancer. *Anticancer Res* 2012;32:5521-6.
10. Syrigou EI, Karapanagiotou EM, Alamara CV, Boura PG, Saif MW, Syrigos KN. Hypersensitivity reactions to oxaliplatin: a retrospective study and the development of a desensitization protocol. *Clin Colorectal Cancer* 2009;8:106-9.
11. Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol* 2006;17:259-61.
12. Shao YY, Hu FC, Liang JT, Chiu WT, Cheng AL, Yang CH. Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc* 2010;109:362-8.
13. Seki K, Senzaki K, Tsuduki Y, Ioroi T, Fujii M, Yamauchi H, et al. Risk factors for oxaliplatin-induced hypersensitivity reactions in Japanese patients with advanced colorectal cancer. *Int J Med Sci* 2011;8:210-5.
14. Polyzos A, Tsavaris N, Gogas H, Souglakos J, Vambakas L, Vardakas N, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology* 2009;76:36-41.
15. Kim MY, Kang SY, Lee SY, Yang MS, Kim MH, Song WJ, et al. Hypersensitivity reactions to oxaliplatin: clinical features and risk factors in Koreans. *Asian Pac J Cancer Prev* 2012;13:1209-15.
16. Kim BH, Bradley T, Tai J, Budman DR. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology* 2009;76:231-8.
17. Gowda A, Goel R, Berdzik J, Leichman CG, Javle M. Hypersensitivity reactions to oxaliplatin: incidence and management. *Oncology (Williston Park)* 2004;18:1671-5; discussion 6, 80, 83-4.
18. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003;89:477-81.
19. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574-80.
20. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* 2009;123:1262-1267.e1.
21. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* 2004;95:370-6.
22. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393-9.
23. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* 2012;129:443-7.
24. Garufi C, Cristaudo A, Vanni B, Bria E, Aschelter AM, Santucci B, et al. Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003;14:497-8.
25. Wong JT, Ripple RE, MacLean JA, Marks DR, Bloch KJ. Vancomycin hypersensitivity: synergism with narcotics and "desensitization" by a rapid continuous intravenous protocol. *J Allergy Clin Immunol* 1994;94:189-94.
26. Zhao M, Isami K, Nakamura S, Shirakawa H, Nakagawa T, Kaneko S. Acute cold hypersensitivity characteristically induced by oxaliplatin is caused by the enhanced responsiveness of TRPA1 in mice. *Mol Pain* 2012;8:55.
27. Descoeur J, Pereira V, Pizzoccaro A, Francois A, Ling B, Maffre V, et al. Oxaliplatin-induced cold hypersensitivity is due to remodelling of ion channel expression in nociceptors. *EMBO Mol Med* 2011;3:266-78.