

## Hypersensitivity reactions to carboplatin and cisplatin in non-small cell lung cancer

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### ABSTRACT

Non-small cell lung cancer (NSCLC) treatment has changed in the past ten years due to the acceptance of platinum-based adjuvant chemotherapy. In the event of relapse, patients are often retreated with platinum agents. Hypersensitivity reactions to carboplatin are well documented among gynecologic oncology patients. Now that adjuvant chemotherapy is a component of NSCLC treatment, platinum hypersensitivity is also a concern in the lung cancer population. A 74-year-old male developed relapsed NSCLC two years after a lobectomy and adjuvant chemotherapy including carboplatin. He was treated with a carboplatin containing regimen, and experienced hypersensitivity during his 2<sup>nd</sup> cycle (post-relapse). We briefly report four additional cases of platinum sensitivity in NSCLC patients, to highlight the increasing likelihood of platinum hypersensitivity in this “at risk” group. Hypersensitivity reactions to platinum chemotherapeutics occur in NSCLC patients, and patients and treating medical staff should be aware of this serious, treatment-related complication.

### KEY WORDS

Carboplatin; cisplatin; hypersensitivity; lung cancer; adjuvant chemotherapy

*J Thorac Dis 2013;5(2):E53-E57. doi: 10.3978/j.issn.2072-1439.2012.06.12*

### Introduction

Lung cancer is the leading cause of cancer death among men and women in the United States (1). During the past ten years, treatment for early-stage and locally advanced non-small cell lung cancer (NSCLC) has changed as the results of large clinical trials have demonstrated a survival benefit from the use of adjuvant chemotherapy, typically 4 cycles of chemotherapy containing a platinum agent, which are given after recovery from surgical resection (2-5). A recent meta-analysis estimated a 5.4% overall survival benefit at 5 years among NSCLC cancer patients receiving adjuvant chemotherapy (6). Due to this change in lung cancer treatment, patients may now receive more than one course of platinum chemotherapy in their lifetime: after the initial surgical resection as adjuvant chemotherapy, and then

later in the event of recurrent or metastatic cancer. Platinum hypersensitivity has been well characterized in the ovarian cancer population, with those patients treated for relapsed disease, after prior exposure to platinum chemotherapy, being at particularly great risk for experiencing a reaction (7,8). Accordingly, doctors and nurses caring for cancer patients should also be aware of the potential for platinum hypersensitivity in the lung cancer population.

### Case

Our case is a 74-year-old caucasian male with a past medical history of stage IIB NSCLC (adenocarcinoma) who was treated with lobectomy in April 2006. Surgery was followed by adjuvant chemotherapy with carboplatin (AUC5) and paclitaxel (175 mg/m<sup>2</sup>) given for 4 cycles, which he completed in August 2006. Additionally, the patient had a history of hypertension, and transitional cell carcinoma of the bladder that was removed via transurethral resection (TURBT), and then treated with intravesicular Bacillus Calmette-Guerin (BCG) infusions. His father died from an unknown type of leukemia while in his eighties. The patient smoked roughly one pack of cigarettes daily for 50 years, quitting in 2006.

In December 2008, the patient was found to have lung nodules on a surveillance computed tomography (CT) scan which

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Submitted May 15, 2012. Accepted for publication Jun 21, 2012.  
Available at [www.jthoracdis.com](http://www.jthoracdis.com)

ISSN: 2072-1439

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**Table 1.** Summary of additional platinum hypersensitivity reactions in patients with NSCLC observed in our institution.

Age/Gender, Stage, Primary treatment, Allergic history	Initial platinum-containing regimen	Re-treatment regimen	Setting of hypersensitivity	Symptoms
56M Stage IIA Lobectomy 9/12/07 NKDA	10/17/07-12/19/07 cisplatin 75 mg/m <sup>2</sup> docetaxel 75 mg/m <sup>2</sup> 4 cycles	8/14/09 cisplatin 75 mg/m <sup>2</sup> pemetrexed 500 mg/m <sup>2</sup>	9/4/09 Cycle 2 of re-treatment (6th cycle overall)	Chest pressure, cough, flushing
53M, Stage IIA Lobectomy 9/1/09 NKDA	10/26/09-1/8/09 cisplatin 75 mg/m <sup>2</sup> docetaxel 75 mg/m <sup>2</sup> 4 cycles	9/15/10 cisplatin 50 mg/m <sup>2</sup> etoposide 50 mg/m <sup>2</sup>	10/13/10 Cycle 2 of re-treatment (6th cycle overall)	Cough, urticaria, pruritis
62F Stage IV NKDA	11/20/09-3/3/10 carboplatin (AUC5) pemetrexed 500 mg/m <sup>2</sup> bevacizumab 15 mg/kg 6 cycles	10/10/10 carboplatin (AUC5) pemetrexed 500 mg/m <sup>2</sup>	11/1/10 Cycle 2 of re-treatment (8th cycle overall)	Chest pressure, dyspnea, cough, flushing
71F Stage IV amoxicillin/clavulanate	9/22/08-1/8/09 carboplatin (AUC5) pemetrexed 500 mg/m <sup>2</sup> bevacizumab 15 mg/kg 6 cycles	8/25/11 carboplatin (AUC5) pemetrexed 500 mg/m <sup>2</sup>	9/14/11 Cycle 2 of re-treatment (8th cycle overall)	Chest pressure, dyspnea

were biopsy proven to represent recurrence of his lung cancer. He then began treatment with intravenous carboplatin (AUC 5), pemetrexed (500 mg/m<sup>2</sup>) and bevacizumab (15 mg/kg). During the second cycle of this chemotherapy regimen he received pemetrexed over 15 minutes, followed by a 1 hour infusion of bevacizumab, and then carboplatin. Twenty-five minutes into the carboplatin infusion (his sixth lifetime exposure to carboplatin), the patient described feeling warmth in his head, and this sensation was closely followed by chest pressure and rigors. He denied shortness of breath or pruritis. Vital signs at the time of symptom onset revealed a temperature of 36 degrees C, blood pressure 146/88 mm Hg, pulse 109 bpm, respiratory rate of 22, pulse oxygenation 98% on room air. Physical examination was notable for tachycardia, generalized flushing, and urticaria on his chest and back. The carboplatin infusion was stopped, and the patient received an infusion of normal saline as well as intravenous diphenhydramine (25 mg) and methylprednisolone (100 mg). His symptoms resolved without further intervention, and vital signs recorded 1 hour after intravenous steroid administration were stable with blood pressure 123/73 mmHg and pulse 69 bpm. Carboplatin was removed from further cycles of chemotherapy.

Just prior to the reaction, the patient's laboratory data revealed a creatinine of 0.8 mg/dL (estimated GFR >60 mL/min) and total bilirubin of 0.7 mg/dL. His regular medication included folic acid 1mg po daily, valsartan 80 mg/hydrochlorothiazide

12.5 mg daily, prochlorperazine 10 mg po as needed for nausea, and dexamethasone 4 mg po, taken the evening before and morning of chemotherapy as premedication. The patient had no known drug allergies prior to the described reaction.

Four additional lung cancer patients at our institution experienced hypersensitivity to a platinum agent (Table 1). In these cases, patients received an initial course of four to six cycles of platinum-based doublet chemotherapy, then had an extended break from chemotherapy (7 to 32 months), and were retreated with a platinum-doublet upon disease relapse or progression. Hypersensitivity reactions were all documented during the 2<sup>nd</sup> cycle of their retreatment courses.

## Discussion

Carboplatin and cisplatin have established themselves as efficacious chemotherapeutics, with utility in treating many solid tumors. Both carboplatin and cisplatin are platinum complexes, exerting their anticancer properties through formation of DNA adducts (9). Allergic responses in industrial workers exposed to platinum salts have been reported since 1945 (10) and allergic hypersensitivity reactions to platinum chemotherapeutics are widely reported, with much of the pertinent literature focused upon carboplatin hypersensitivity in setting of ovarian cancer treatment (11).

Hypersensitivity reactions to the platinum compounds are

largely consistent with type 1, IgE mediated hypersensitivity, associated with repeated exposure to the agent. IgE is believed to act upon tissue mast cells and basophils in peripheral blood, prompting the release of histamines, leukotrienes and prostaglandins (12). These reactions are typified by capillary dilation and the rapid contraction of smooth muscle, often resulting in a rash (urticaria), flushing, and pruritis. In more severe cases (NCI CTCAE v4 Grade 3-4) angioedema, symptomatic bronchospasm, hypotension, and cardiac dysfunction may be evident, warranting immediate intervention (13). Symptoms usually develop during or within a few hours of drug infusion, but may occur 1-2 days after administration (7).

A ten-year study of carboplatin hypersensitivity in ovarian cancer patients reported an incidence rate of 16% (14), whereas a lower rate of 4.6% was found among patients at our institution between 2006 and 2010 (15). While estimates of the overall incidence of carboplatin hypersensitivity vary, it is important to understand that the cumulative incidence of carboplatin hypersensitivity increases considerably in proportion to the number of cycles administered (9). Patients receiving five or fewer cycles of carboplatin were reported to have a 0.92% incidence rate of hypersensitivity, with the cumulative risk increasing to 19.5% among patients who have received eight cycles (9). Markman, *et al.*, noted that, in his study population, 50% of carboplatin hypersensitivity episodes occurred during course eight of platinum therapy, with some of the observed patients receiving cisplatin and then carboplatin in prior to the reaction (7).

Patients who receive first-line platinum-based chemotherapy, and then are treated again with a platinum agent at the time of relapse, are at the greatest risk of experiencing hypersensitivity. In a small study population of relapsed ovarian cancer patients, as many as 44% of patients who were given a second and third cycle of carboplatin, post-relapse, developed hypersensitivity (8). A more recent paper noted carboplatin hypersensitivity in 21.7% of patients treated for recurrent ovarian cancer. Of those who experienced a reaction, 86.7% did so during the second cycle of chemotherapy post-relapse, with prolonged retreatment interval (time elapsed between end of front-line therapy and beginning of carboplatin retreatment) having independent predictive value. Patients with a retreatment interval >23.4 months had an approximately seven-fold greater likelihood of developing a hypersensitivity reaction (16). Other studies have reported carboplatin-free intervals of >12 (17) or >13 months, as well as a cumulative carboplatin dose of >650 mg, as independent predictors of carboplatin hypersensitivity (18). The largest study of carboplatin hypersensitivity in the setting of recurrent ovarian cancer was published in 2011, involving over 900 patients. This study reports an overall hypersensitivity rate of 23.6% when carboplatin-based chemotherapy is re-introduced (19). Patients with a history of systemic allergic reactions to medication or environmental exposure also have a significantly increased risk of

hypersensitivity (20).

Hypersensitivity reactions to cisplatin are also documented. An early study evaluating cisplatin in combination with vindesine as treatment for lung cancer described that, among patients receiving six or more cycles of combination chemotherapy, five of 21 patients experienced "anaphylaxis" characterized by urticaria, pruritis, respiratory distress, and mild hypotension within 10 minutes of the administration of cisplatin. In all cases the reaction subsided upon cessation of the cisplatin infusion and administration of epinephrine and diphenhydramine (21). Four cases of cisplatin hypersensitivity in ovarian cancer patients were later reported, two of which took place during the fifth administration of cisplatin. In another case the patient received three cycles of cisplatin following a debulking procedure, and experienced a reaction two years later when cisplatin treatment was resumed upon discovery of metastatic disease. A different patient, who received front-line carboplatin, relapsed after a six year treatment free interval and experienced cisplatin hypersensitivity on the third cycle of retreatment (22).

Intradermal skin testing has been used to predict hypersensitivity to carboplatin, with a very low false-negative rate of 1.5% (23). While a negative skin test may provide reassurance before administering carboplatin to at risk patients, the implications of a positive skin test are less clear. Changing to an alternative platinum agent following a reaction, e.g., switching from carboplatin to cisplatin after negative skin testing, has been reported (24). However, skin testing is not done at our institution and discontinuation of platinum chemotherapy entirely appears to be the most reasonable decision in the lung cancer patients who experience hypersensitivity. Platinum desensitization protocols, requiring inpatient hospitalization, are carried out for ovarian cancer patients who may benefit from continued platinum chemotherapy (25), however, such efforts would not typically be warranted in the setting of palliative chemotherapy for metastatic or recurrent lung cancer.

Three of our patients experienced a hypersensitivity reaction upon their sixth exposure to a platinum agent, with the last two patients experiencing a reaction on the eighth total exposure. In all cases, the patients received an initial course of four to six cycles of platinum-based doublet chemotherapy, then had an extended break from chemotherapy (7 to 32 months), and were retreated with a platinum-doublet upon disease progression. Hypersensitivity reactions all were documented during the second cycle of their retreatment courses, after a platinum-free interval.

The last two cases in the table did not receive adjuvant chemotherapy, but illustrate an analogous situation that may occur in the setting of patients who present with stage IV disease. These patients were treated initially with platinum-doublet chemotherapy, and were later re-challenged with a platinum agent after progressing through subsequent lines of non-platinum

therapy. Such scenarios, with prolonged survival and preserved performance status in stage IV disease, allowing multiple opportunities for platinum treatment, should become more commonplace as lung cancer patients derive benefit from new targeted therapies. Lastly, although we have no cases to illustrate this patients with stage III disease who receive neoadjuvant chemotherapy, or concurrent chemotherapy and radiation containing a platinum agent, would in principle, carry a similar future risk of platinum hypersensitivity if treated with a platinum chemotherapeutic for relapsed disease. The overall incidence of platinum hypersensitivity among lung cancer patients at our institution has not yet been determined.

## Conclusions

These cases illustrate that NSCLC patients may experience hypersensitivity reactions to both carboplatin and cisplatin, and such reactions occur in a pattern consistent with that described by the gynecologic oncology literature. Patients who have previously received multiple exposures to platinum chemotherapy are at risk of a reaction, and those patients who are beginning platinum-based chemotherapy for relapsed cancer (after a prior exposure to platinum chemotherapy and a treatment-free interval) are at great risk. All “at risk” lung cancer patients must be counseled extensively about the risk of platinum hypersensitivity, and be aware of the symptoms they should report to their treatment team. Clinicians and infusion center nursing staff should be aware of these risks and be able to respond urgently in the event of a reaction, and these patients should be scheduled for chemotherapy only during times where a physician is readily available.

## Acknowledgements

**Disclosure:** The authors declare no conflict of interest.

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**Cite this article as:** Randall JM, Bharne AA, Bazhenova LA. Hypersensitivity reactions to carboplatin and cisplatin in non-small cell lung cancer. *J Thorac Dis* 2013;5(2):E53-E57. doi: 10.3978/j.issn.2072-1439.2012.06.12