Carboplatin Hypersensitivity in Recurrent Ovarian Cancer

PAULA J. ANASTASIA, RN, MN, AOCN®

From Cedars-Sinai Medical Center, Los Angeles, California

Author's disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Paula J. Anastasia, RN, MN, AOCN®, 8700 Beverly Boulevard, Suite 290W, Los Angeles, CA 90048.
E-mail: paula.anastasia@cshs.org

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Women with newly diagnosed with ovarian cancer (and fallopian tube and primary peritoneal) are commonly treated with combination chemotherapy consisting of IV carboplatin and a taxane. Patients who are platinum-sensitive (disease-free interval of greater than 6 months) have a longer survival advantage over patients who are platinum-resistant (disease-free interval of less than 6 months) (National Comprehensive Cancer Network, 2011). Retreatment with a platinum-based therapy is often the treatment of choice when a patient is platinum-sensitive and has recurrent disease. Carboplatin is often used because it has less nephrotoxicity, neurotoxicity, and emetogenicity than cisplatin (Parmar et al., 2003). Increased risks for carboplatin hypersensitivity reactions (HSRs) include the total number of prior carboplatin-based treatments, a platinum-free interval of greater than 13 months, and reexposure and retreatment with carboplatin (Gadducci et al., 2008; Makrilia, Syrigou, Kaklamanos, Manolopoulos, & Saif, 2010; Navo et al., 2006).

Incidence

Unlike paclitaxel HSRs, which usually occur during the first or second dose, carboplatin HSRs are rare with the first course of treatment (Robinson et al., 2001). The incidence of carboplatin HSR is reported from 1% to 44%, with an estimated 27% occurrence with seven cycles or more, and up to 44% reported in third-line treatment. Less than 1% occur in the first 1 through 5 cycles (Markman et al., 1999; Rose, Fusco, Smrekar, Mossbruger, & Rodriguez, 2003; Sliesoraitis & Chikhale, 2005). Cisplatin HSR has a reported incidence of 5% to 20%, with the average incidence occurring between the fourth and eighth cycles. It should be noted that several studies have shown success in substituting cisplatin after a carboplatin HSR. However, one study documented a fatality, recognizing that although rare, the incidence of cross-allergy remains unknown (Dizon, Sabbatini, Aghajanian, Hensley, & Spriggs, 2002). Increased HSR has also been documented with cisplatin and radiation (Koren et al., 2002).

Oxaliplatin, another platinum-based chemotherapeutic agent, is indicated for colorectal cancer (CRC) but has been used in ovarian cancer treatment, especially as a substitute in platinum-sensitive patients who have experienced HSRs with first- and second-generation platinums (Ferrandina et al., 2007; Gutierrez, Pautier, & Lhomme, 2002). The incidence of oxaliplatin HSR in patients with CRC has

Case Study

Mrs. A.Z. is a 61-year-old Caucasian woman who was diagnosed with stage IV (pleural effusion cytology positive), grade 3, papillary serous adenocarcinoma of the ovary at age 56. She underwent standard of care procedures with an optimally debulked surgery, followed by IV paclitaxel and carboplatin every 3 weeks. Her CA-125 was elevated prior to surgery and had a slower than expected decline to normal values (< 35 U/mL) even after 6 cycles of chemotherapy. Her medical oncologist made the decision to give three more cycles of chemotherapy and reevaluate with a computerized axial tomography (CT) scan. During the ninth cycle of chemotherapy, 1 hour after completion of paclitaxel and 15 minutes into her last carboplatin infusion, Mrs. A.Z. reported erythema of the palms, throat tightness, and abdominal pain. The carboplatin infusion was stopped. The patient was given additional dexamethasone and an antihistamine. The symptoms resolved immediately and the decision was made to discontinue further carboplatin. Her medical oncologist recommended 8 monthly cycles of PLD for "mild stranding around the bowel," which was seen on CT scan. Her CA-125 remained in the upper limits of normal. Mrs. A.Z. tolerated PLD for 8 months without significant adverse events.

Mrs. A.Z. presented to our facility for a second opinion, 2 months after completing her eighth PLD. Her CA-125 continued to increase and her medical oncologist told her she had limited options because she was platinum resistant and platinum allergic. After a thorough patient history, physical, and review of her previous scans with the radiologist, treatment options were discussed, including using a platinum-based regimen since her last platinum was 9 months prior. Mrs. A.Z. verbalized fear and apprehension regarding receiving a platinum-based regime, despite the rationale of a desensitization regime. She chose to transfer her care to our practice and agreed to enroll in a clinical trial consisting of weekly paclitaxel and a targeted agent. She remained on the clinical trial for 10 months, and was taken off due to rising CA-125, even though the CT scan remained stable. Again, discussion regarding different treatment options included a nonplatinum single-agent chemotherapy or a combination platinum-based treatment. She agreed to be treated with a carboplatin substitute and her next treatment would consist of cisplatin 35 mg/m^2 and gemcitabine 800 mg/m^2 IV on days 1 and 8 in a 21-day cycle.

Mrs. A.Z. was instructed to premedicate with oral dexamethasone 20 mg, 12 hours and 6 hours prior to infusion. She would receive additional IV dexamethasone 20 mg prior to cisplatin infusion, in addition to oral loratidine 10 mg (she stated diphenhydramine causes "restlessness") and cimetidine 300 mg IV. She also received antiemetic coverage with a long-acting 5-HT$_3$ antagonist and NK1 receptor antagonist. A 4-mg oral dexamethasone taper was given on days 2 and 3 following chemotherapy. The infusion nurse was informed about Mrs. A.Z.'s prior allergic reaction that occurred more than 2 years ago in another facility. No skin testing was done on Mrs. A.Z. prior to her cisplatin. Skin testing is per physician discretion and not a standard protocol at our facility. An emergency kit was available at Mrs. A.Z.'s bedside, including oxygen. There was no HSR after six complete cycles of cisplatin and gemcitabine using this aggressive premedication regime. Mrs. A.Z.'s follow-up PET/CT showed no evidence of disease.

Nine months later, after another relapse of her disease, Mrs. A.Z. started oral chemotherapy with altretamine (Hexalen). She tolerated it for 5 months, then requested a change due to chronic nausea. Once again the decision to reintroduce carboplatin was discussed, this time in combination with PLD. Data from Pujade-Lauraine et al. (2010) reported less HSR with carboplatin when combined with PLD, and Mrs. A.Z. did tolerate PLD in the early part of her diagnosis, which was the reason to repeat this agent. Realizing Mrs. A.Z. was at risk for another carboplatin HSR, she was premedicated with the same regime used with her prior cisplatin and gemcitabine. The carboplatin dose was decreased to AUC 5 instead of 6 when given in combination of PLD. It was also infused over 3 hours instead of 1 hour, which is consistent with rapid desensitization schedules (O'Cearbhaill et al., 2010).

Mrs. A.Z. received two cycles of PLD and carboplatin without incident. Her CA-125 had decreased after both cycles, which validated response to treatment. On cycle 3, Mrs. A.Z. received carboplatin prior to PLD, and within 15 minutes of the infusion she reported pal-

mar itching and burning, throat tightening, and abdominal pain. The infusion was immediately stopped. Oxygen saturation was 92% then increased to 95%. The physician was called and 50 mg of diphenhydramine was administered, despite the patient's history of restlessness with drug. Her vital signs stabilized and she reported feeling better immediately. After 30 minutes of observation, it was decided to hold carboplatin, despite stabilization, and proceed with the planned PLD. She tolerated the PLD without incidence.

One month later, Mrs. A.Z. returned for her next cycle of chemotherapy. She was switched to PLD 30 mg/m^2 and cisplatin 50 mg/m^2 every 4 weeks (Table 1). She was instructed to premedicate the day before with oral dexamethasome 20 mg, 12 hours and 6 hours prior to infusion. On the day of infusion she received IV dexamethasone 20 mg, IV ranitidine 50 mg, and oral loratadine 10 mg. The PLD was administered prior to cisplatin. An additional dose of 8-mg dexamethasone IV was infused prior to cisplatin. Mrs. A.Z. tolerated her platinum-based chemotherapy without incident. She was instructed to begin an oral dexamethasone 4-mg taper on days 2 and 3, along with follow-up with her primary care physician to monitor glucose levels. In addition, she was instructed to call with any allergy-like symptoms or unresolved nausea, vomiting, and fever.

been reported from 12% to 18.9%, with less than 2% causing grade 3 or 4 events (Saif, 2006; Shibata et al., 2009). The incidence of oxaliplatin HSR in patients with ovarian cancer is unknown at this time. However, in our facility, when a patient has shown favorable platinum-based responses and then had subsequent HSRs to carboplatin and cisplatin, oxaliplatin has been the substituted platinum of choice.

Risk factors for carboplatin HSR include prior exposure and retreatment with IV carboplatin (as opposed to intraperitoneal adminis-

Table 1. Case Study Summary

Date	Diagnosis	Treatment	Outcome
11/06	Stage IV ovarian cancer	Surgery followed by chemotherapy	Optimal debulk
11/06–5/07		Paclitaxel and carboplatin x 9	Regimen #1 chemotherapy Allergic reaction with cycle 9 of carboplatin Completion of paclitaxel
5/07–1/08	Residual disease on CT	Pegylated liposomal x 8 Doxorubicin (PLD)	Regimen #2 chemotherapy Stable disease
3/08–1/09	Persistent disease Elevated CA-125	Weekly paclitaxel and experimental agent	Regimen #3 Progressive disease
2/09–8/09	Persistent disease	Cisplatin and gemcitabine x 6	Regimen #4 Premedicated No allergic reaction Remission
5/10–9/10	Recurrent disease	Altretamine	Regimen #5 Chronic nausea
10/10	Persistent disease	Carboplatin/PLD	Regimen #6
11/10		Carboplatin/PLD	Premedicated No allergic reaction
12/10		Carboplatin/PLD	Carboplatin reaction despite premedication Tolerated PLD
1/11	Chemo regime #6 resumes	Cisplatin/PLD	Premedicated No allergic reaction

tration), personal history of other drug allergies, and asthma diagnosis (NCCN, 2011). In a study by Pujade-Lauraine and colleagues (2010), the combination of carboplatin and pegylated liposomal doxorubicin (PLD) was compared to carboplatin and paclitaxel in platinum-sensitive recurrent ovarian cancer, revealing an improved side-effect profile with the PLD combination. The doublet of carboplatin plus PLD reported a 5.6% incidence of HSR compared to 18.8% with carboplatin and paclitaxel.

Etiology

The cause of carboplatin HSR is not clearly understood. Several authors (Navo et al., 2006; Sliesoraitis & Chikhale, 2005) have hypothesized that the cause is due to type I IgE-mediated reactions, which trigger the release of histamine and inflammatory mediators such as prostaglandin D2, leukotriene C4, interleukins 4 and 13, and tumor necrosis factor alpha, resulting in immediate symptoms. Type IV reactions will manifest as a delayed onset of symptoms and result from T cells recognizing antigens through receptors that bind to the major histocompatibility complex at the surface of an antigen-presenting cell. Patients may be initially sensitized, then require additional drug recognition such as is seen after readministration of carboplatin in recurrent ovarian cancer (Navo, et al., 2006; Makrilia, Syrigou, Kaklamanos, Manolopoulos, & Saif, 2010). Consulting with an allergist may be a reasonable intervention. The use of a leukotriene inhibitor (montelukast sodium) can reduce swelling and may be recommended. Additionally, it has been suggested that a nonmeasurable contaminant, such as metallic platinum, may be responsible for the HSR, which has been documented as an occupational hazard for platinum miners (Williams & Markman, 2009; Zanotti, et al., 2001). Therefore, patients who may have this as an occupational exposure, may potentially have an increased risk for a carboplatin HSR.

Manifestations of HSR

Development of symptoms can vary from subtle to extreme, and may occur within minutes, hours, or days after the infusion (Gadducci et al., 2008). Mild HSRs include skin rash, palmar itching or burning, hives/pruritus, edema of the face and hands, abdominal and/or back pain, nausea, and diarrhea (NCCN, 2011; Makrilia et al., 2010) Severe reactions may present as bronchospasms, tachycardia, hypertension, or hypotension. In the case of severe and life-threatening symptoms, further exposure to the drug should be discouraged (O'Cearbhaill et al., 2010; NCCN, 2011). The National Cancer Institute (NCI) has a Common Terminology Criteria for Adverse Events (CTCAE) to help with documentation consistency (Table 2).

Patients should always be informed by the prescribing physician and advanced practice clinician that retreatment with carboplatin may cause an allergic reaction. Patients should be reassured that emergency practices will be in place and that most of these reactions are mild and manageable. If a HSR reaction does occur, the infusion should be stopped immediately, followed by assessment of vital signs, infusion of normal saline, and notification of the physician and the advanced practice clinician. For mild reactions, stopping the infusion may cause resolution of the symptoms. If symptoms persist, administration of normal saline, corticosteroids, and an antihistamine should be ordered. An H_2 receptor antagonist, such as ranitidine or cimetidine, may provide added relief of an allergic reaction, in addition to activating the acid-producing parietal cells of the stomach.

Desensitization Protocol

Retreatment with a platinum agent subsequent to a HSR involves gradual reintroduction of the drug, while escalating to full dose. Desensitization protocols vary and can include the use of premedications or dilution regimens where a drug ratio of 1:1,000 is administered over an hour, then the dilution is decreased each hour (Winkeljohn & Polovich, 2006). Several authors have used desensitization protocols with mixed success (Table 3). Prolonged desensitization regimens are usually time consuming, and unless the facility has a 24-hour infusion center, the treatment requires an inpatient admission (McElroy, von Gruenigen, & Waggoner, 2003). The day before the carboplatin infusion, patients are generally premedicated with a corticosteroid and an antihistamine.

Rapid desensitization protocols have also been attempted with mixed success (O'Cearbhaill, 2010). Castells et al. (2008) reported a 94% success, evidenced by mild or no reactions in 413

Table 2. Grading of Common Adverse Events

Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Flushing, rash, fever < 38˚C, no intervention	Infusion stopped, intervention responds to treatment (i.e., antihistamines); recovers within 24 h	Prolonged or delayed response to medications; brief interruption of infusion then recurrence of symptoms; may require hospitalization; organ complications (i.e., renal impairment)	LIfe-threatening events; emergent interventon	Death
Anaphylaxis	–	–	Bronchospasm, possible uticaria, IV intervention, allergy-related edema, hypotension	Life-threatening events; emergent intervention	Death
Cytokine release syndrome	Mild, no intervention	Infusion stopped, intervention responds to treatment; recovers within 24 h	Prolonged or delayed response to medications; brief interruption of infusion then recurrence of symptoms; may require hospitalization; organ complications (i.e., renal impairment)	Life-threatening events; emergent intervention	Death
Infusion-related reaction	Mild, no intervention	Infusion stopped; intervention responds to treatment; recovers within 24 h	Prolonged or delayed response to medications; brief interruption of infusion then recurrence of symptoms; may require hospitalization; organ complications (i.e., renal impairment)	Life-threatening events; emergent intervention	Death
Pruritus	Mild/localized, may require topical ointment	Intense or widespread; intermittent; causes skin changes from scratching; requires systemic intervention	Constant, intense or widespread; interferes with ADL or sleep; corticosteroid or systemic immunosuppressive treatment required	–	–

Note. ADL = activities of daily living. Adapted from National Cancer Institute: Common Terminology Criteria for Adverse Events (NCI, 2010)

Table 3. Desensitization Regimens

	Patients	Premedication regimen	Duration	Success rate
O'Cearbhaill (2010)	174	Dexamethasone 20 mg po night before and prior to carbo; immediately prior to carbo, diphenhydramine 50 mg IV, ranitidine 50 mg IV	3 h	96.6%
Abe (2010)	3	Dexamethasone 20 mg, promethazine 50 mg, ranitidine 50 mg	2 d	100%
Hesterberg (2009)	30	Fexofenadine 180 mg po and/or desloratadine 5 mg po bid, dexamethasone 10 mg po	11 h	99%
Castells (2008)	60	Diphenhydramine 25 mg po/IV or famotine 20 mg IV, or ranitidine 50 mg IV, and prn lorazapam 0.5–1 mg IV	3.8–5.8 h	88.1%
Confino-Cohen (2005)	23	Dexamethasone 8–12 mg IV, ondansetron IV	6 h	86.9%
Lee (2005)	31	Diphenhydramine 25 mg IV, famotidine 20 mg IV, lorazepam 1 mg	5.8 h	80%
Markman (2004)	5	Zileuton 600 mg po qid (5 days), montelukast sodium 10 mg po qd (5 days), indomethacin 50 mg po tid (1 day), albuterol sulfate 8 mg po bid (1 day), famotidine 20 mg IV, dexamethasone 20 mg IV, diphenhydramine 50 mg IV	90 min	80%
Rose (2003)	33	Dexamethasone 20 mg po or IV 6 hours before, dexamethasone 20 mg IV, and diphenhydramine 50 mg IV 30 min before	16.5 h	79%

Note. Adapted from Makrilia et al. (2010).

patients using a standardized 12-step rapid desensitization. The patient population included patients who had HSRs to various agents including platinums, paclitaxel, liposomal doxorubicin, and rituximab (Rituxan). However, 59 of these patients had HSRs to carboplatin, and 1 to cisplatin. Their protocol involved 12 consecutive steps at increasing infusion rates. Since there is no one standard of care desensitization protocol, practices may individualize and modify a prolonged and rapid desensitization regimen to provide safety outcomes for their patient

Skin Testing

The role of routine carboplatin skin testing remains undecided. There are numerous publications supporting its use in patients who have had previous carboplatin HSR, and the authors favor implementing it as a standard procedure in patients prior to their eighth dose of carboplatin, when a reaction is most likely to occur (Markman et al., 2003; Sliesoraitis & Chikhale, 2005; Zanotti et al., 2001;). It should be noted that patients may still have a HSR when the skin test is negative, as may patients who have gone through a desensitization protocol (Makrilia et al., 2010.) A skin test involves an intradermal injection of a 0.02-mL undiluted aliquot of carboplatin on the surface of the arm. A wheal greater than 5 mm and a flare surrounding the area translates to a positive skin test (Winkeljohn & Polovich, 2006).

Discussion

Real-life scenarios do not always the follow the textbook. For instance, by definition, Mrs. A.Z., the patient profiled in the case study, is not platinum-sensitive, as she had persistent disease after her initial platinum-based chemotherapy in 2006. However, she continued to respond to platinum agents, and thus maintain survival. For all oncology nurses, including advanced practice clinicians, it is essential to follow safety standards and understand which agents have an increased risk of HSR. In addition, educating the patient and instituting early intervention and emergency procedures is critical when a patient with recur-

rent ovarian cancer is going to be retreated with carboplatin. Advanced practice clinicians are also in the position to be familiar and up to date with the data, which encourages collaboration with the physician with respect to the patient's treatment decisions.

The risk of a HSR is a serious and potentially life-threatening event. The benefits must supersede risks when exploring options for patient care. Whether development of a desensitization protocol is implemented, or a published protocol is modified, evidence-based medicine should be included in the patient's plan of care. Education should be provided to the infusion nurses so that emergency measures are maintained in the event of a HSR. The advanced practice clinician or the physician should be available while the patient is receiving retreatment with carboplatin. For some practices, especially those with limited staff or resources, admitting the patient to the medical intensive care unit may provide improved monitoring of the patient who is be rechallenged or desensitized for a HSR.

In our setting, a modified protocol per O'Cearbhaill et al. (2010) is often used with success. Patients are premedicated the day before with 20-mg oral dexamethasone at 12 hours and 6 hours prior to carboplatin infusion. Extra doses of IV dexamethasone 20 mg, an antihistamine, an H_2 antagonist, and antiemetics are infused prior to carboplatin. The carboplatin dose is infused slowly during the first hour at 1 cc/h, with completion of the infusion over the next 2 hours. Although Mrs. A.Z. was unable to continue treatment with carboplatin, due to a recurrent HSR, she is benefitting from the substituted version of cisplatin. The advanced practice clinician can maintain a leadership role by educating and supporting staff, and continuing as patient advocate when patients have challenging treatment options.

DISCLOSURES

The author has no conflicts of interest to disclose.

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