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Case report

Successful resuscitation after cardiac arrest secondary to carboplatin infusion: A case report

Madushka Y. De Zoysa[a], Nicole A. Nakamaru[a], Samantha B. Kaiser[a], Marcia A. Ciccone[a], Laila I. Muderspach[a,b], Koji Matsuo[a,b,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, CA, USA
[b] Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA

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1. Background

Ovarian cancer is the deadliest gynecologic cancer and the fifth leading cause of cancer-related death among women in the United States (Siegel et al., 2017). Most women are diagnosed in their 60s to 70s, with over 70% presenting with advanced-stage disease (Cristea et al., 2010). Though most experience remission with comprehensive treatment, the majority of women with advanced-stage disease recur. The mainstay of treatment for such recurrent disease is generally salvage chemotherapy (Matsuo et al., 2010).

Per the National Comprehensive Cancer Network (NCCN) guidelines, platinum-based chemotherapy agents such as carboplatin are the first-line treatment choice in women with ovarian cancer. Used since the 1970s, platinum-based chemotherapy agents doubled the response rate seen with single-agent non-platinum based drugs (Cristea et al., 2010). Commonly documented adverse reactions to platinum agents include nausea, bone marrow suppression, nephrotoxicity, and neurotoxicity (Zweizig et al., 1994). Carboplatin hypersensitivity reactions, though rare, occur in 1–20% of patients, typically presenting after repeated courses of carboplatin over times due to antigen recall (Sood et al., 1995; Markman et al., 1999). Symptoms of anaphylaxis are the most common indicators of a reaction. Though cardiac arrest has been reported as a result of an anaphylactic carboplatin reaction, it has never been documented as an immediate manifestation of such a reaction. Adverse reactions must be weighed against the benefits of continuing chemotherapy with prudent consideration of alternative therapies.

This case report describes a patient with recurrent ovarian cancer who experienced a cardiac arrest immediately after carboplatin infusion and was successfully resuscitated with high-quality cardio-pulmonary resuscitation.

2. Case report

A 71-year-old Caucasian female with recurrent stage IIIC high-grade papillary serous adenocarcinoma of the ovary presented to our institution's chemotherapy infusion center for her scheduled carboplatin/gemcitabine infusion. She had a history of chronic kidney disease and transient asymptomatic tachycardia; she had completed a full work-up with cardiology and had no acute condition. Holter monitoring performed 12 months prior demonstrated intermittent runs of tachycardia and bradycardia, occasional ventricular ectopic beats, and frequent supraventricular ectopic beats; otherwise, no remarkable abnormal finding. Echocardiogram demonstrated a normal ejection fraction of 60–65% with no wall motion abnormalities.

Her initial oncologic treatment included an optimal cytoreductive surgery followed by six cycles of adjuvant carboplatin area-under-curve (AUC) 5 and paclitaxel 175 mg/m^2 both on day 1 of a 21 day cycle. Following therapy, she was declared to have no evidence of disease and was followed per routine surveillance protocol.

Approximately one year later, however, the patient's CA-125 levels rose to 31 U/mL and computer tomography (CT) scan demonstrated recurrence with pleural nodules, diaphragmatic lymphadenopathy, hepatic metastases, mesenteric soft tissue nodules, and enlarged pelvic lymph nodes. The patient underwent six cycles of carboplatin AUC 5

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Southern California, 2020 Zonal Avenue, IRD520, Los Angeles, CA 9033, USA.
E-mail address: koji.matsuo@med.usc.edu (K. Matsuo).

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and liposomal doxorubicin 30 mg/m^2 on day 1 of a 28 day cycle with interval improvement of hepatic and peritoneal disease. She then started maintenance therapy with single-agent liposomal doxorubicin (40 mg/m^2, day 1 of 28 day cycle) with disease stability for 24 cycles. However, repeat imaging demonstrated new hepatic lesions, worsening retroperitoneal and mediastinal lymphadenopathy, and multiple peritoneal nodules.

Three cycles of carboplatin (AUC 4, day 1 of 28 day cycle) resulted in continued worsening of disease. The patient then began experimental protocol but progressed after only two cycles. She subsequently failed paclitaxel (80 mg/m^2, every week) with bevacizumab (10 mg/kg, every two weeks), nivolumab (3 mg/kg, every two weeks), and gemcitabine (800 mg/m^2, every 2 weeks). Prior to completing the first cycle of cyclophosphamide (50 mg, orally daily) and bevacizumab (10 mg/kg, every two weeks), significantly elevated blood pressures and acute kidney injury necessitated discontinuation of the regimen.

With few remaining options, carboplatin (AUC2, every 2 weeks) and gemcitabine (500 mg/m^2, every 2 weeks) were started. On day 15 of the first cycle, the patient was pre-medicated with famotidine 20 mg, ondansetron 16 mg, and dexamethasone 10 mg, all given intravenously 30 min prior to starting chemotherapy. She declined the prescribed diphenhydramine. Within a few minutes of beginning the carboplatin infusion, the patient became unresponsive without preceding signs or symptoms of anaphylaxis as witnessed by the nurse at the bedside. At this time, a Code Blue was called. Bedside chest compression and bag mask ventilation were immediately initiated. The cardiac monitor displayed pulseless electrical activity; thus, physicians administered intravenous epinephrine. After 24 minutes of resuscitative effort, including four rounds of cardio-pulmonary resuscitation, intubation, 4 mg of epinephrine, and one dose each of calcium chloride, sodium bicarbonate, and atropine, the code team achieved return of spontaneous circulation. She was subsequently transported to the intensive care unit for further evaluation and treatment.

Both chest CT and electrocardiogram returned unremarkable. Findings on CT head and brain magnetic resonance imaging failed to account for her arrest, and repeat cardiac imaging, performed due to her history of tachycardia, demonstrated stability. Of note, a potassium level drawn the day prior to infusion was slightly elevated (5.6 mmol/L). She had been treated with oral kayexalate on the day of her infusion just prior to the arrest event, and her potassium level was within normal limits at the time of intensive care unit arrival. The remainder of her hospital course was uneventful. She was extubated on hospital day 3 and deemed stable for discharge on hospital day 11. She did not have any neurologic sequelae from the arrest.

After recovering from this episode, she wished to try further salvage therapy and started rucaparib (600 mg, orally twice daily) based on a recently detected somatic BRCA2 mutation. However, she eventually succumbed to progressive ovarian cancer and died four months after the episode of cardiac arrest.

3. Discussion

Delayed anaphylactic reactions to carboplatin are relatively common in patients who have previously tolerated the agent, classically occurring during the second cycle of a second course of treatment or on the 8th cycle of primary therapy. They are thought to be type I IgE-mediated reactions, but they may also occur *via* direct release of vasoactive particles (Sood et al., 1995; Markman et al., 1999; Robinson et al., 2001). In contrast to paclitaxel reactions, which are usually characteristic, platinum reactions present with variable symptomatology and timing of onset. Symptoms can range from mild pruritis to cardiac arrest, as experienced in our case, and though they typically occur during infusion, reactions occurring several days after infusion have also been reported (Markman et al., 1999).

Risk factors contributing to a delayed platinum hypersensitivity reaction include longer platinum-free interval and higher initial total dose (Koshiba et al., 2009; Sugimoto et al., 2011). Our patient had received 15 total cycles of carboplatin during the course of her treatment, and she was given additional treatment after to a long platinum-free interval with the thought that there may be some degree of re-sensitization given her extremely limited options. Cardiac arrest occurred during infusion of her 16th cycle. Given our patient's cumulative risk factors for a delayed hypersensitivity reaction, bronchospasm and hypotension secondary to an anaphylactic reaction may explain her cardiac arrest.

Two prior cases note circulatory collapse unresponsive to resuscitative efforts as a result of anaphylaxis. The first patient experienced seizure activity as an initial carboplatin reaction. This patient was re-challenged with cisplatin resulting in hypotension and bradycardia unresponsive to resuscitation (Zweizig et al., 1994). Dizon et al. reported a similar case of cisplatin re-challenge after a documented carboplatin allergy resulting in anaphylaxis refractory to resuscitative efforts (Dizon et al., 2002). A third report noted hypotension and syncope prior to cardiac arrest requiring intubation and intensive care unit admission after carboplatin administration (Watanabe et al., 2005).

Another explanation for sudden cardiac arrest could be carboplatin-induced vasospasm. This occurred in one documented case of cardiac arrest associated with carboplatin infusion. This patient experienced severe chest pain followed by cardiac arrest and death beginning 5 minutes after the start of carboplatin infusion. Authors attributed this case to acute coronary syndrome, though no autopsy was performed (Gadducci et al., 2008). They also cited two other instances of coronary vasospasm in response to carboplatin infusion, one in which transient ST segment elevation was noted during the event, but no abnormalities were noted on follow up angiography (Chasen and Ebrahim, 2002), and another in which similar changes were noted on electrocardiogram (ECG) in a lung cancer patient experiencing chest pain during a carboplatin infusion (Yano and Shimada, 1996). An ECG performed after our patient was resuscitated showed sinus tachycardia without ST segment changes, though this does not rule out a transient cardiac event, especially given her pre-existing cardiac comorbidities. The likelihood of a cardiac event is further supported by her pre-treatment mild hyperkalemia, which may have been exacerbated by her chronic kidney disease and platinum-induced nephrotoxicity (Bashir et al., 2007).

In summary, carboplatin hypersensitivity reactions may vary widely in presentation and can include sudden cardiac arrest. Premedication with dexamethasone and diphenhydramine may prevent some but not all incidences of allergic reaction. Due to this risk, preparation and vigilance for such catastrophic events are needed when administering repeated courses of platinum agents, especially with the second dose of a recurrent treatment. A fully stocked crash cart should be readily available, and providers should be certified in advanced cardiac life support protocols. Furthermore, patients should be made aware of the risk of hypersensitivity. If a reaction occurs, further treatment may be undertaken with desensitization (O'Malley et al., 2017; Robinson et al., 2001). However, it may be prudent to discontinue the offending agent permanently in the case of severe reactions such as the one experienced by our patient.

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