Carboplatin Hypersensitivity Reactions

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Carboplatin is used widely to treat cancers such as lung, breast, and ovarian. Hypersensitivity reactions (HSRs) to carboplatin can occur, often after numerous doses. The reactions can range from mild to life threatening. Oncology nurses witness the reactions and are instrumental in providing interventions to assist patients. Symptoms include flushing, rashes, itchy palms, nausea, difficulty breathing, back pain, hypotension, and tachycardia. Interventions include support of patients with oxygen and IV hydration along with administration of certain medications to diffuse HSRs. Predictive measures may include skin testing on patients who have received more than seven total doses of carboplatin. Desensitization protocols may be useful for patients with positive skin tests. Ultimately, with the potential for life-threatening reactions, patients and physicians need to consider the risk-to-benefit ratio of using the drug.

Case study: B.A. is a 62-year-old female who had a total abdominal hysterectomy and bilateral salpingo-oophorectomy for stage III epithelial ovarian cancer two years ago. She received six cycles of paclitaxel and carboplatin. After her second-look exploratory surgery, all of her biopsies were negative. Now she has ascites, which, upon diagnostic paracentesis, shows recurrent ovarian cancer. She has received two cycles of paclitaxel and carboplatin and is due for her third dose (ninth total dose) of carboplatin. She received IV dexamethasone 20 mg, famotidine 20 mg, diphenhydramine 50 mg, and granisetron 1 mg as premedications prior to infusion of paclitaxel. After 10 minutes of the carboplatin infusion, she states, “I don’t feel good.” She reports itchy palms, tightness in her chest, difficulty catching her breath, back pain, and sudden nausea. Assessment of vital signs shows a heart rate of 115, blood pressure of 108/50, and oxygen saturation of 86% on room air. After the carboplatin is stopped, interventions include IV dexamethasone 20 mg and diphenhydramine 50 mg, administration of oxygen at 2 L by nasal cannula, and an IV bolus of 500 cc of normal saline. She recovers after one hour, with normalization of vital signs and oxygen levels. Her physician decides to discontinue carboplatin and continue with single-agent paclitaxel.

Nurses working with patients receiving carboplatin may not realize the potential for hypersensitivity reactions (HSRs). This article focuses on a review of carboplatin HSRs, including signs and symptoms and management strategies. Information about how to predict and prevent reactions will be discussed. Nurses can become instrumental in assessing for and implementing safety guidelines in their practice settings to address carboplatin HSRs.

Review of Hypersensitivity Reactions

Nurses often administer chemotherapy drugs that have potential for HSRs. Drugs such as paclitaxel, rituximab, and bleomycin sulfate are known for their risks of HSRs. Newer agents such as cetuximab and bevacizumab also have the potential. With this known hypersensitivity potential, nurses are aware of, plan for, and take action to decrease such risk. Action includes administrating premedications such as diphenhydramine and dexamethasone, slowing initial rates of infusion, and monitoring patients closely for signs and symptoms of HSRs.

Unexpected HSRs often are frightening to nurses and patients when they occur. As seen in the case study, carboplatin HSRs can occur without warning after numerous doses. In fact, that is a defining characteristic of carboplatin HSRs. Because of the unpredictable nature of carboplatin HSRs, many nurses and patients are unprepared when they occur. When reactions occur days after infusion, nurses may miss...
the opportunity to recognize them. In addition, many nurses and physicians may attribute mild HSRs to other medications, such as paclitaxel.

Platinum reactions have occurred in men working in platinum salt refineries. They developed symptoms of allergic reactions, often after one or two years of exposure (Zanotti et al., 2001). Such reactions are thought to be type I HSRs, in which platinum causes a release of vasoactive substances (Jones, Ryan, & Friedlander, 2003). The process causes symptoms such as asthma, rhinitis, and contact dermatitis (Zanotti et al.). Further exposure to platinum salts only continues to cause HSRs in refinery workers.

Type I HSRs occur following exposure to an antigen, which results in the formation of an immune globulin E (IgE) antibody (Johnson & Peebles, 2004). Type I HSRs commonly are seen in people who experience reactions to bee stings. On further exposure to a specific antigen (such as carboplatin), the IgE complexes bind to the surfaces of mast cells and basophils. The binding to the cells causes them to release certain mediators, such as histamine, leukotrienes, and the cytokines interleukin and tumor necrosis factor (Anand & Routes, 2004). The mediators and cytokines cause vasoconstriction, airway constriction, increased mucous production, urticaria and angioedema, nausea, vomiting, and diarrhea. If significant vasodilation and vascular permeability occur, hypotension can lead to vascular collapse. Without prompt intervention and patient support, death can occur.

Platinum Agents

Carboplatin was developed after cisplatin and was approved by the U.S. Food and Drug Administration in 1989 for treatment of ovarian carcinoma (Sood, Gelder, Huang, & Morgan, 1995). Carboplatin has a more favorable side effect profile than cisplatin, with less nausea and vomiting, minimal hair loss, and less neurotoxicity and nephrotoxicity (Markman et al., 1999). Carboplatin can be administered over 15–30 minutes, unlike cisplatin, which requires vigorous hydration, monitoring of intake and output, and an administration rate of no more than 1 mg per minute (Cleri & Haywood, 2002).

Since its development, carboplatin has been used in many tumor types, such as ovarian, lung, and breast cancer. Along with the increased use has come an increase in the occurrence of HSRs. The reported rate of HSRs varies from 5%–34% (Dizon, Sabbatini, Aghajanian, Hensley, & Spriggs, 2002). HSRs often are not seen until after multiple courses of treatment. Reports of HSRs occurring in patients after the 8th and 13th doses of carboplatin have been documented (Weidmann, Mulleneisen, Bojko, & Niederle, 1994). Polyzos et al. (2001) reported an HSR rate of 16% among women being treated for ovarian cancer. The reactions occurred after the fifth, sixth, seventh, and eighth courses of carboplatin.

Cisplatin also causes HSRs. Meyer, Zuberbier, Worm, Oettle, and Reiss (2002) found a rate of 5% mild to life-threatening HSRs for both carboplatin and cisplatin. Other research has shown reactions to cisplatin when it was substituted for carboplatin, often after patients had HSRs to carboplatin. Dizon et al. (2002) reported treating seven patients with cisplatin after they experienced HSRs to carboplatin. Of the seven patients, five (71%) were successfully retreated with cisplatin. One patient developed an HSR that warranted stopping cisplatin permanently, and the other had an HSR that progressed to cardiac arrest and death. Jones et al. (2003) described the experience of five patients with ovarian cancer who had previous HSRs to carboplatin and were retreated with cisplatin for recurrent disease. Of the five patients, two (40%) had HSRs that warranted stopping cisplatin. Death has been reported in a patient receiving cisplatin for the treatment of recurrent ovarian cancer (Zweigiz, Roman, & Muderspach, 1994).

Symptoms and Management of Carboplatin Hypersensitivity Reactions

Carboplatin HSRs can show a varied pattern of presentation after numerous courses of treatment. The reactions can be classified as acute (occurring during administration) or delayed (following administration) (Robinson et al., 2001). Nurses see the acute reactions because they occur in the office or hospital. Nurses should be cognizant of delayed reactions and assess patients by reviewing side effects at their next treatments. Nurses must be alert to symptoms of rash, flushing, or itching, which can occur days after infusion and can signal HSR.

Acute symptoms of carboplatin HSRs include flushing, dyspnea, back pain, nausea, vomiting, and itching, especially of the palms of hands and soles of feet (Robinson et al., 2001). Other symptoms can occur, such as bronchospasm, throat and chest tightness, tachycardia, hypotension, and possible respiratory arrest (Polyzos et al., 2001). Patients often tell nurses that they just do not feel well or speak of a feeling of “impending doom,” which is difficult to describe but present and real to patients.

Symptoms often resolve after treatment, although they may cause distress for patients. Nurses must be aware of the severity of the reactions. Supportive care includes vigorous hydration and frequent monitoring. Treatment includes administration of dexamethasone, diphenhydramine, epinephrine, or a combination. On rare occasions, patients may need intensive support as described in the following published case report (Sood et al., 1995). A patient had been previously treated with carboplatin for ovarian cancer. Upon presentation with recurrent disease, the patient was treated with paclitaxel and carboplatin. During the second infusion of carboplatin, she became anxious and dyspneic.
after 15 minutes of infusion. The carboplatin was stopped, but the patient became cyanotic, obtunded, tachycardic, and hypoten-

tive. She required intubation and treatment with IV fluids, epinephrine, dopamine, diphenhydramine, and hydrocortisone. Eventually, she was extubated and recovered. She continued to receive paclitaxel as single agent for her disease.

After reading the case report, some may question whether the patient had a reaction to the paclitaxel and not the carboplatin. Some distinctions exist between HSRs caused by the two drugs. With paclitaxel, the timing of a reaction is generally predict-
able. In a report by Weiss et al. (1990), of 32 HSRs to paclitaxel, 18 occurred with the first dose of paclitaxel, 13 occurred with the second dose, and only one occurred during the sixth dose. With carboplatin, reactions occur after many doses of the drug, generally more than six.

Paclitaxel reactions occur within minutes of starting infusion (Weiss et al., 1990). With carboplatin, reactions can be seen at any time during infusion or even hours and days after. HSRs from either drug can cause similar symptoms, and both drugs can cause reactions despite adequate premedication. Generally, with paclitaxel HSRs, patients can be rechallenged with the drug, usually following additional premedication. Switching to cisplatin can be an option after carboplatin HSR, but cross-
sensitivity has occurred. Depending on the type and severity of reactions to carboplatin, patients and healthcare providers have to weigh the risks versus benefits of rechallenging with a potentially life-threatening drug.

Preparation prior to infusion of carboplatin, or any chemo-

therapy drug, should include an allergy history that covers medications and environmental allergens. Patients and families should be taught about the potential for reactions and the in-
terventions used to treat reactions. Patient teaching will help patients recognize how they may feel and what therapeutic options may be needed. The options may include restarting infusion or rechallenging. If skin testing is implemented, nurses should teach patients about the reason for it, why it is needed, and what results may indicate. Nurses should formulate or become familiar with their institutions’ anaphylaxis protocols and be able to locate any emergency equipment needed.

Because carboplatin HSRs can be mild or severe, nurses must recognize and begin prompt support and treatment. Upon recognition of a suspected HSR, carboplatin infusion should be stopped and infusion of normal saline maintained. Once carboplatin infusion is stopped, assessment should include checking patients’ vital signs and oxygen saturation. Airway, breathing, and circulation should be assessed and maintained. A physician should be notified as soon as possible. Medical management includes IV hydration to increase blood pressure and adminis-

tration of oxygen. If bronchoconstriction occurs, epinephrine and diphenhydramine will aide with bronchodilation. If available, mini-nebulizer treatments with a drug such as albuterol may assist with bronchodilation. Dexamethasone can be given to ameliorate the total inflammatory response caused by the release of cytokines. Nausea, caused by release of histamine, can be managed with antiemetics such as promethazine and prochlorperazine. H₂ blockers such as cimetidine can help to reduce acid secretions from the stomach (see Table 1). Patients often do not feel well after HSRs and warrant close observation for hours afterward.

Table 1. Medications and Indications for Carboplatin Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>MEDICATIONS</th>
<th>INDICATION(S)</th>
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<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Diminishes release of cytokines from mast cells</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Anti-emetic, anxiolytic potential</td>
</tr>
<tr>
<td>Albuterol inhaler</td>
<td>Bronchodilator</td>
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<tr>
<td>Famotidine and cimetidine</td>
<td>Inhibits gastric acid secretion</td>
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<tr>
<td>Prochlorperazine and promethazine</td>
<td>Anti-emetics; control nausea and vomiting</td>
</tr>
<tr>
<td>Normal saline IV</td>
<td>Adds volume to vascular system and maintains or increases blood pressure</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Stimulates alpha receptors causing peripheral vasconstriction, increasing blood pressure</td>
</tr>
<tr>
<td>Topical steroid creams</td>
<td>Reduces inflammation from rash</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Sympathomimetic stimulation, bronchodilation, and decongestion</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Maintains adequate oxygen levels</td>
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</table>

Note. Based on information from Robinson et al., 2001; Spratto & Woods, 2003.

Methods to predict and prevent carboplatin HSRs can be found in the literature. Skin testing to determine risk of HSRs is explained in the literature (Markman et al., 2003; Zanotti et al., 2001). The test uses 0.02 ml of undiluted aliquot of carboplatin on the volar surface of the arm (Markman et al., 2003). A positive test is a wheal of greater than 5 mm and a flare surrounding it. Of the 39 patients with positive skin test results, 7 elected to proceed with carboplatin infusions. Of them, six experienced HSRs, which were not severe. The remaining 32 patients with positive skin tests elected not to receive further carboplatin. Therefore, a positive skin test may be a predictor of potential HSR, but it does not necessarily predict the severity of reaction if it does occur.

In another study of skin testing involving 47 patients, 13 (28%) experienced positive skin tests after a median of nine
courses of carboplatin (Zanotti et al., 2001). Each patient who had undergone more than seven cycles of carboplatin received an intradermal skin test. A positive test was considered a wheal of 5 mm with a surrounding flare. Of the 15 patients who had positive skin reactions, four elected to receive additional carboplatin. The other nine elected to forego carboplatin. Of the four patients who elected to be treated despite positive skin tests, three had HSRs varying from mild to moderate in severity. Only two patients who had negative skin tests experienced HSRs. In the study, negative skin tests predicted reactions accurately in 166 of 168 courses of chemotherapy.

Nurses may be asked to participate in desensitization protocols. Desensitization is administering an allergen (such as carboplatin) in small doses until the full dose is achieved, hopefully without creating an anaphylactic reaction (De Maria, Lebel, Desroches, & Gauvin, 2002). Desensitization protocols involve the infusion of doses of carboplatin at a slow rate with adequate premedication. The two types of desensitization protocols described in the literature include those that use premedications and those that use dilution regimens.

Robinson et al. (2001) achieved a success rate of 94% in preventing HSRs with IV and oral administration of premedications. Desensitization premedication regimens have used IV dexamethasone 10–20 mg every six hours, cimetidine 300 mg every eight hours, and diphenhydramine 25–50 mg every six hours. Other IV premedications may include ondansetron or granisetron for control of nausea. Oral agents also can be used. Patients are instructed to start oral medications at home prior to infusion.

One suggested dilution regimen involves mixing small amounts of carboplatin in normal saline (1:1,000 dilution) and infusing over one hour. If that is tolerated well, carboplatin mixed at a ratio of 1:100 dilution then is administered over one hour. If that is tolerated, a dilution of 1:10 is infused over one hour. Finally, the full remaining dose is given over one hour. One problem with the regimen is the time commitment necessary. The dilutional schedule can take as long as six additional hours to complete. Desensitization protocols do not necessarily prevent carboplatin HSRs.

**Conclusion**

Nurses can be leaders by teaching physicians and patients about the potential of HSRs with carboplatin. Physicians must weigh the risks of possible reactions with the benefits that patients may receive from treatment with carboplatin. Nurses need to be aware of the potential for reactions and teach patients about symptoms to report, especially in the days following infusion. Nurses, together with physicians, must develop standing orders to manage carboplatin HSRs. Nurses may collaborate with physicians in instituting skin testing for patients at a certain point in their treatment, such as when they reach the seventh total carboplatin dose. If reactions occur, nurses may participate in desensitization protocols. Finally, nurses should work with staff to implement a plan for managing HSRs when patients require treatment in an acute setting.

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**References**


