Chemotherapy Hypersensitivity Reactions in Ovarian Cancer

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Abstract

Ovarian cancer is the fifth leading cause of cancer death among women in the United States. Chemotherapy using a taxane and platinum combination is key in improving survival in patients with newly diagnosed advanced ovarian cancer and is also used to treat recurrent platinum-sensitive disease. However, hypersensitivity reactions (HSRs) to chemotherapeutic agents are increasingly common and can greatly limit their use. Moreover, because of the frequent lack of equally effective alternative agents, chances of survival can be compromised. Therefore, physicians caring for these patients must be familiar with the management of HSRs to chemotherapeutic agents.

Four types of drug HSRs have been well characterized. Type I, drug-specific IgE antibodies coat the surface of mast cells and basophils. On antigen binding, cross-linking occurs and cell activation ensues, causing the immediate release of mediators, such as histamine and tryptase, responsible for the classic signs and symptoms of those reactions (Table 1). Mast cell and basophil degranulation can also be triggered by nonspecific pathways, such as complement activation, creating a clinical picture identical to classic type I reactions. Regardless of the underlying mechanism, these reactions have the potential to lead to anaphylaxis.

Ovarian cancer is the leading cause of death among gynecologic malignancies and ranks fifth in overall cancer-related mortality among women in the United States. Chemotherapy, particularly with a taxane and platinum combination, is key to improving survival in patients with advanced newly diagnosed ovarian cancer and in those with recurrent cancer that remains sensitive to platinum. However, adverse reactions to these drugs can greatly limit their use and, because of the frequent lack of equally effective alternative agents, patients’ chances of survival may be compromised. Recent advances have been made in the management of chemotherapy hypersensitivity reactions (HSRs), especially in ovarian cancer, that for some patients offer promise for circumventing those reactions.

Four types of drug HSRs have been well characterized. In type I, drug-specific IgE antibodies coat the surface of mast cells and basophils. On antigen binding, cross-linking occurs and cell activation ensues, causing the immediate release of mediators, such as histamine and tryptase, responsible for the classic signs and symptoms of those reactions (Table 1). Mast cell and basophil degranulation can also be triggered by nonspecific pathways, such as complement activation, creating a clinical picture identical to classic type I reactions. Regardless of the underlying mechanism, these reactions have the potential to lead to anaphylaxis. Type I reactions are the most common HSRs seen in patients with ovarian cancer, and are also referred to as allergic or infusion reactions. Type II reactions involve antibody-mediated cytotoxicity (eg, drug-induced immune hemolytic anemia), and type III are mediated by
and platinum drugs and the recommended approach for patients experiencing these reactions.

**Acute Management of HSRs**

HSRs to chemotherapy are unpredictable, can occur suddenly, and may deteriorate quickly. Therefore, patients must be educated to recognize and report any symptom of HSR (Table 1) so that treatment can be instituted in a timely manner. The nursing staff and clinicians caring for those patients should be prepared to treat these reactions with short notice. For that purpose, chemotherapy infusion units should be adequately equipped to perform resuscitation maneuvers, and standing orders should be written to ensure rapid administration of drugs, such as epinephrine, in case of anaphylaxis.

HSRs may manifest with a variety of symptoms (Table 1) and may vary in severity from isolated flushing to anaphylaxis (Table 2). In any case, the drug infusion should be immediately stopped. Anaphylaxis should be diagnosed when 2 of the following organ systems exhibit signs and symptoms of mast cell activation: skin (flushing, urticaria, angioedema), respiratory (dyspnea, wheeze, stridor, hypoxemia), cardiovascular (reduced blood pressure, syncope), and gastrointestinal (persistent crampy abdominal pain, vomiting). Anaphylaxis should be treated immediately and initially with intramuscular epinephrine. The patient should then be placed in the recumbent position with lower extremities elevated (except if respiration is compromised or the patient is vomiting). Supplemental oxygen and intravenous fluids should be administered if needed. H₁ and H₂ blockers are routinely administered as adjunct to epinephrine. Inhaled short-acting β-agonists can also be used to complement epinephrine in treating bronchospasm.

Corticosteroids are typically given to prevent the late-phase reaction of anaphylaxis. Measurement of serum tryptase, the major protease released from mast cells along with histamine during an anaphylactic reaction, at 1 to 6 hours after the reaction is a useful indicator of anaphylaxis because it supports a causal role for mast cells in the reaction, as exemplified in Table 3. Nonanaphylactic HSRs can usually be managed with antihistamines (H₁ and H₂ blockers) and corticosteroids (methylprednisolone, hydrocortisone, dexamethasone).
The subsequent management of HSRs depends on the drug being administered and the severity of the initial reaction (Table 2) in accordance with the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer (Figures 1 and 2). Recommendations made in the NCCN Guidelines regarding management of HSRs were all category 2A because they emerged from a uniform consensus and were based on lower-level evidence.

Platinum Drugs: Carboplatin and Cisplatin

Cisplatin was the first commercialized platinum drug, and early studies reported an incidence of HSRs ranging from 1% to 20%. In the 1990s, carboplatin gradually replaced cisplatin in ovarian cancer treatment because of its better safety profile (less nephrotoxicity, neurotoxicity and severe emesis vs cisplatin). Because of its remarkable efficacy in first-line, second-line, and salvage therapy for ovarian cancer, carboplatin became increasingly used, leading to a dramatic increase in the rate of HSRs. The incidence of carboplatin HSRs increases with the number of cycles received, averaging 1% in those receiving 6 cycles or less but reaching 47% in those receiving 7 cycles or more. On average, patients react on the eighth or ninth overall cycle of platinum drug—a situation often leading to discontinuation of the drug.

Clinical Features

HSRs to platinum drugs generally occur during the drug infusion, although sometimes onset can be delayed for minutes, hours, and sometimes even days after the end of the infusion. Signs and symptoms reflect mast cell and basophil activation (Table 1). Cutaneous symptoms are present in most HSRs to carboplatin, most frequently as flushing accompanied by pruritus (affecting all 60 patients in 1 cohort). In that same study, cardiovascular symptoms (most commonly chest pain and presyncope) were present in 57% of patients, gastrointestinal symptoms (including nausea, vomiting, diarrhea) in 42%, respiratory symptoms (most commonly dyspnea) in 40%, and throat tightness in 25%. It has been reported that patients with a severe carboplatin HSR

| Table 2 Allergy Severity Grading of Hypersensitivity Reactions |
|-----------------|-----------------|-----------------|-----------------|-------------------|
| Grade 1         | Pruritus, flushing, urticaria, angioedema, maculopapular rash | None            | None            | None              |
| Grade 2         | Same as grade 1 but not required | Nausea, abdominal pain | Dyspnea, sneezing/nasal congestion, coughing | Chest pain, tachycardia, hypertension |
| Grade 3         | Same as grade 1 but not required | Vomiting, diarrhea | Bronchospasm, laryngeal edema, desaturation | Hypotension, presyncope, syncope, sense of impending doom |
| Grade 4         | Same as grade 1 but not required | Same as grade 3 but not required | Respiratory failure | Cardiovascular collapse |


| Table 3 Elevation of Serum Tryptase After an IgE-Mediated Reaction to Carboplatin |
|-----------------|-----------------|-----------------|
| Patient | Skin Test | Serum Tryptase (mg/L) |
| A     | +            | 31               |
| B     | +            | 47               |

*Upper limit of normal: 11.4 mg/L.

often had experienced minor symptoms, such as a mild rash and/or pruritus, during the previous infusion of the drug, which had been overlooked. These findings emphasize the need to educate patients to recognize and report any symptoms they might experience after a chemotherapy infusion, particularly involving a platinum agent.

**Mechanisms of HSRs**

HSRs to platinum drugs are IgE-mediated allergies, as supported by several lines of evidence. Platinum salts have long been recognized as a cause of IgE-mediated allergy in precious metal refinery workers, eliciting mainly respiratory symptoms such as asthma and rhinitis. Platinum drugs, such as carboplatin, cisplatin, and oxaliplatin, are made with those salts, and multiple cycles of these drugs are necessary to elicit a reaction, suggesting that an immunologic sensitization process must occur before a reaction results. A standard way of demonstrating IgE-mediated allergies is through skin testing, which introduces a small amount of allergen through the skin, activating local mast cells in sensitized patients and resulting in a wheal and flare reaction. Skin testing is positive in most patients who will or have experienced an HSR to platinum drugs, but not in tolerant subjects. Also, tryptase is increased in the serum of patients after a reaction, showing mast cell activation (Table 3). Rapid drug desensitization, a procedure that can be used to administer a drug causing an IgE-mediated allergy in a particular patient, has been shown to be very effective in preventing HSRs to platinum drugs and to temporarily blunt skin test reactivity to the inciting agent. Finally, oxaliplatin- and carboplatin-specific IgEs have recently been found in patients with a documented HSR to those drugs.

**Figure 1** Management of hypersensitivity reactions to platinum drugs in ovarian cancer patients. Reaction grades are defined in Table 2. Abbreviations: IV, intravenous; IP, intraperitoneal. Adapted from Morgan RJ Jr, Armstrong DK, Alvarez RD, et al. NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 1, 2014. Available at: NCCN.org. Accessed May 17, 2013.
Risk Factors

One of the most decisive factors influencing the occurrence of HSRs to platinum drugs is the total number of cycles the patient has received, with reactions occurring on average during the eighth or ninth overall cycle.\(^7,8,15,17,18\) Similarly, patients experiencing these reactions were shown to have received a higher cumulative dose of carboplatin (3850 vs 1792 mg).\(^14\) Also, an interval greater than 12 months between 2 treatments with a platinum agent increases the incidence and severity of HSRs.\(^14,16,29\) One study showed that reactions occurred with an incidence of 25.8%, of which 6.5% were severe, in patients who had an interval of less than 12 months between treatments, whereas reactions occurred with an incidence of 59.2%, of which 47.0% were severe, in patients with an interval of greater than 24 months.\(^16\) Intrapерitoneal infusions can trigger infusion reactions, although the associated risk seems to be lower than with the intravenous route and the number of cycles necessary to elicit a reaction is greater.\(^30\) A history of allergic disorders, particularly of drug allergy, seems to increase the risk of HSRs to platinum drugs.\(^7,14,16\) Furthermore, combining carboplatin with pegylated liposomal doxorubicin (PLD) seems to significantly reduce the incidence of HSRs attributable to carboplatin compared with administering carboplatin as a single agent or in combination with paclitaxel.\(^31,32\) The effect of PLD on reducing carboplatin-related infusion reactions remains to be determined. Finally, a recent study showed that a deleterious BRCA1/2 mutation status was an independent risk factor for carboplatin HSRs (odds ratio, 13.1; 95% CI, 2.6–65.4) and that HSRs occurred after a lower cumulative exposure in those patients.\(^33\)

Figure 2 Management of hypersensitivity reactions to taxanes, pegylated liposomal doxorubicin, other chemotherapeutic drugs, and monoclonal antibodies patients with in ovarian cancer. Reaction grades are defined in Table 2.

\(^{a}\)Grade 2 reactions without cardiovascular or respiratory involvement.

\(^{b}\)Grade 2 reactions with cardiovascular or respiratory involvement.

Abbreviations: IV, intravenous; IP, intraperitoneal.

Prevention of HSRs

The incidence of HSRs to carboplatin rises sharply after 7 cycles of a platinum drug and most patients who are allergic to carboplatin have a positive skin test to the drug. Therefore, Markman et al examined the utility of carboplatin skin testing before each drug infusion (with a concentration varying between 5 and 12 mg/mL) starting at the seventh cycle to preemptively identify patients with an allergy. A total of 126 patients had 717 skin tests, of which 39 were positive. Among those 39 patients, 6 of 7 who went on to receive a regular carboplatin infusion reacted, suggesting a high positive predictive value for carboplatin skin testing. In contrast, 7 of 87 patients with a negative skin test experienced an HSR during regular infusion, all of which were mild and limited to cutaneous manifestations. However, because of its impracticality and the limited evidence supporting its use, preemptive skin testing is not widely used.

In an effort to reduce the incidence of HSRs during a second treatment with carboplatin, O’Cearbhaill et al prophylactically treated 174 patients with a prolonged 3-hour infusion of carboplatin and a premedication regimen consisting of 2 doses of oral dexamethasone at 20 mg beginning the night before the infusion, and H₂ and H₃ blockers given intravenously 30 minutes before the infusion from the ninth cycle of carboplatin onward. When compared with a group of 533 patients who received carboplatin through regular infusion, the incidence of HSRs significantly decreased from 21% to 3% and onset was delayed until after a median of 9 to 16 cycles of carboplatin. However, these results from a single-center retrospective trial have yet to be confirmed prospectively.

Management of HSRs

The recommended management of HSRs to platinum drugs shown in Figure 1 is in accordance with NCCN Guidelines. In contrast to other drugs used in ovarian cancer, HSRs to platinum drugs occur almost exclusively through an IgE-mediated mechanism, with several important clinical implications. Previous exposure is necessary to elicit an immune response, leading to the production of IgE. Therefore, HSRs occurring on first exposure to platinum drugs are unlikely to be IgE-mediated, except in rare instances when patients have been exposed to platinum salts through their occupation, such as jewelry makers. Thus mild HSRs occurring in truly platinum-naïve patients during the first infusion of a platinum drug can be reasonably treated with antihistamines and a decrease in the infusion rate. On the other hand, once a patient has been exposed to any platinum salt–containing molecule, allergic sensitization is possible and HSRs after the infusion of platinum drugs are likely the sign of an IgE-mediated allergy. Importantly, IgE-mediated allergies are not safely prevented by premedication with corticosteroids and antihistamines or by a slower infusion rate (except if it is given in a way that creates desensitization), and fatalities in these circumstances have been reported. Furthermore, mild reactions are often the first signs of allergic sensitization and can be precursors of anaphylactic reactions on reexposure, because an immunologic recall mechanism is implicated.

Patients with HSR to platinum drugs who benefit from this treatment and for which alternative agents are considered less effective and/or more toxic may be referred to an allergist or a specialist with expertise in desensitization for evaluating the possibility of administering further cycles through a desensitization procedure. Otherwise, rechallenge should not be attempted because of the potential harm that might be caused to the patient. Several patients have been transitioned successfully to cisplatin after an HSR to carboplatin, although some patients have had recurrent HSRs. In a cohort of 24 patients with ovarian cancer, 6 (25%) eventually reacted to cisplatin after having reacted to carboplatin and at least 2 fatalities have been reported in such context. Interestingly, skin testing has been used in few patients to predict reactivity to cisplatin after a carboplatin HSR and no patient with a negative skin test to cisplatin has reacted. However, given the limited data available, these decisions are preferably made after evaluation by an allergist or specialist with expertise in this field. Cross-reactivity could also be assessed through drug-specific IgE testing, as suggested by a recent study showing that among 7 patients with carboplatin allergies, 2 had cisplatin-specific IgEs.

Rapid Drug Desensitization

Various desensitization protocols have been used for patients allergic to a platinum drug with variable success rates. If consideration is given to readminister a platinum drug through desensitization, the patient should preferably be referred to...
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an academic center with expertise in desensitization, because those procedures are considered high-risk and must be tightly regulated and performed by allergists or specialists with expertise in desensitization.\(^2\) An example of a desensitization protocol with established safety and efficacy in a large cohort of patients with ovarian cancer with carboplatin HSRs is given in Table 4. From 2000 to 2006, this protocol has been used successfully in 101 patients with carboplatin allergies, for a total of 374 desensitization procedures.\(^7,21,49\) Most patients did not react (67%) or had a mild reaction (27%) during desensitization, despite the fact that 80% had a severe initial HSR to carboplatin.\(^7\) Only 2 patients had to be treated with epinephrine, and both completed their infusion and, after added premedication and protocol modification, could receive further desensitization infusions without breakthrough symptoms.\(^7,49\) The incidence of breakthrough symptoms and their severity steadily decreases with each desensitization, with most reactions occurring during the first and second infusions.\(^7,49\) Furthermore, 75% of breakthrough symptoms occur during the final step of the protocol (step 12).\(^7\) All patients received their full dose of carboplatin under this protocol.\(^7,21,49\) Desensitization should be given thoughtful consideration in patients experiencing an HSR to platinum drugs who are expected to benefit from continued treatment with this drug and for whom alternative agents are considered either less effective and/or more toxic.\(^2\)

### Table 4 Example of 12-Step Brigham and Women’s Hospital and Dana-Farber Cancer Institute Desensitization Protocol for Carboplatin

<table>
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<th>Step</th>
<th>Solution</th>
<th>Rate (mL/h)</th>
<th>Time Per Step (min)</th>
<th>Dose Administered Per Step (mg)</th>
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<td>369.072</td>
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Total time: 339.4 min = 5.7 h

Skin Testing

Skin testing is a useful tool to identify patients allergic to platinum drugs and may be used for risk stratification.\(^7,10,18,23,24\) (Table 5). Depending on the severity of the initial HSR, the time elapsed between the HSR and skin testing, and the concentration used for carboplatin skin testing, between 45% and 88% of patients with a carboplatin HSR will have a positive skin test.\(^7,10,18,23\) Limited data suggest that a positive skin test to carboplatin has a high positive predictive value, because 6 of 7 patients with a positive skin test who went on to receive a regular infusion experienced a reaction.\(^24\) In patients with a negative skin test performed at a concentration of at least 3 mg/mL and a delay of less than 6 months between the HSR and skin testing, HSR on rechallenge has been found to be rare and no severe HSR has been reported.\(^7,10,18,23,24,50\) Importantly, skin test reactivity seems to wane over time, and patients with a delay greater than 6 months between the HSR and skin testing might initially have negative skin test results that will convert to positive results after either 1 or 2 carboplatin infusions.\(^10,18\) Those patients are at risk of a recurrent reaction and may benefit from repeated skin testing up to the third carboplatin re-infusion.\(^18\) In light of these data, it is advisable to reintroduce a platinum drug via desensitization in patients with a positive skin test, whereas rechallenge may be considered in patients with a negative skin test, although these decisions should be made by an allergist or specialist with expertise in this field.\(^2\)

| Table 5 Value of Skin Testing in Patients With a History of Reaction to Carboplatin |
|---------------------------------|-----------------|-----------------|------------------|-------------------|
|                                | Castells et al\(^7\) \(n=60\) | Hesterberg et al\(^19\) \(n=38\) | Patil et al\(^18\) \(n=39\) | Leguy-Seguin et al\(^23\) \(n=8\) |
| Positive ST result (%)         | 53 (88)          | 25 (66)         | 16 (41)          | 6 (75)            |
| Prick                          | 8 (15)           | N/A             | 2 (14)           | 2 (33)            |
| IDR*                           | 45 (85)          | N/A             | 14 (86)          | 4 (67)            |
| Negative ST result (%)         | 7 (12)\(^\text{a}\) | 13 (34)\(^\text{c}\) | 23 (59)\(^\text{a}\) | 2 (25)\(^\text{c}\) |
| ST converter\(^\text{f}\)       | 2 (29)           | 6 (46)          | 12 (52)          | None              |

Abbreviations: IDR, intradermal reaction; N/A, not applicable; ST, skin test.

\(^\text{a}\)Maximal concentration used for IDR: 10, 3, 5, and 1 mg/mL, respectively.

\(^\text{b}\)A total of 4 patients experienced a reaction after receiving the medication without desensitization.

\(^\text{c}\)A total of 11 patients were treated with desensitization and 6 had breakthrough reactions, 5 of which converted to a positive ST result.

\(^\text{d}\)A total of 23 patients were treated with desensitization and 11 had breakthrough reactions, 10 of which converted to a positive ST result. A total of 6 patients with a negative ST result tolerated treatment without desensitization.

\(^\text{e}\)No patient with a negative ST result was reexposed to carboplatin.

\(^\text{f}\)Conversion from a negative to a positive ST result after receiving additional cycles of the drug.

Taxanes: Paclitaxel and Docetaxel

Paclitaxel is a molecule originally derived from the bark of the Pacific yew tree, Taxus brevifolia, and because of its poor solubility is compounded with the solvent Cremophor EL (polyoxyethylated castor oil).\(^52\) The high incidence of HSRs to paclitaxel in phase I trials rapidly lead to the use of a premedication regimen consisting of corticosteroids and antihistamines and a prolonged infusion time.\(^52\)–\(^54\) With these precautions, subsequent trials showed a dramatic reduction in the rate of HSRs to paclitaxel to less than 10% for HSRs of any severity and to approximately 1% for severe HSRs.\(^55\)–\(^61\)

Docetaxel is a semisynthetic taxane derived from the needles of the European yew tree, Taxus baccata, and because of its low solubility is formulated with the solvent polysorbate 80.\(^52\) Initially, the incidence of HSRs averaged 30% and that of fluid retention reached 59% in patients receiving the drug without premedication.\(^62\)–\(^63\) Pretreatment with dexamethasone reduced the incidence of HSRs to between 3.5% and 16.5% and that of fluid retention to between 5.0% and 12.2%.\(^64\)–\(^66\) A direct comparison of infusion reaction rates between paclitaxel and docetaxel, given in combination with carboplatin, revealed that docetaxel caused infusion reactions in 3.5% of patients compared with 1.7% for paclitaxel, despite standard premedication in both groups.\(^64\)

Clinical Features

Reactions to taxanes generally occur within minutes after starting the infusion and during the first 2 cycles of treatment.\(^7,17,67\) The signs and symptoms of these reactions are thought to be the result of mast
cell and basophil activation and are summarized in Table 1. In a cohort of 28 patients with moderate to severe HSRs to paclitaxel, cutaneous symptoms (most commonly flushing) were present in 82% of patients, and cardiovascular symptoms (most commonly chest pain) were present in 75%. Interestingly, severe back pain occurred in 36% of patients, whereas it is rarely seen in HSRs to other chemotherapeutic drugs, for unclear reasons. Importantly, some patients may present with delayed reactions up to 7 days after the infusion, which can be the prelude to a severe immediate reaction during the next infusion.

### Premedication Regimens and Infusion Rates

Premedication with corticosteroids and antihistamines (H₁ and H₂ blockers) is highly effective at reducing the rate of HSRs to paclitaxel. The initial premedication protocol included 2 doses of dexamethasone to be taken the night before and the morning of the infusion, followed by the intravenous administration of H₁ and H₂ blockers 30 to 60 minutes before the infusion. For practical reasons and because of uncertainty about the safety of infusing paclitaxel if the patient had forgotten to take the corticosteroid, a simplified premedication regimen was devised to replace the 2 dexamethasone doses with a single intravenous dose of dexamethasone to be given 30 to 60 minutes before infusion. Several studies showed a similar rate of HSRs (overall and severe) between the standard and the simplified regimen. However, in a retrospective single-center study, Kwon et al. showed that the shorter 1-dose dexamethasone protocol induced HSRs in 17.3% of patients (7.3% severe) compared with 7.5% (0.9% severe) with the 2-dose dexamethasone protocol. Furthermore, one fatality has been reported from an HSR to paclitaxel in a patient pretreated with the simplified regimen. These data strongly support the use of premedication with a combination of corticosteroids and antihistamines before paclitaxel administration, although they do not show superiority of one protocol over the other. Different infusion rates have been used for paclitaxel, ranging from as short as 30 minutes to as long as 24 hours. Williams and Bryant, in a Cochrane meta-analysis, found no significant difference in the rate of HSRs between 3- and 24-hour infusions. Infusion times as short as 1 hour does not seem to increase the incidence of HSRs to paclitaxel.

### Premedication before docetaxel administration

Premedication before docetaxel administration serves 2 purposes: preventing HSRs and reducing fluid retention, which is thought to result from capillary protein leakage. Dexamethasone, 8 mg twice daily for 3 days starting 24 hours before the infusion is usually administered, although a recent study suggested that a single dose of dexamethasone administered 30 minutes before the infusion successfully prevented both HSRs and fluid retention, which occurred in that study in 7.8% and 12.2% of patients, respectively. After uneventful infusions, the dose of corticosteroid might be reduced and eventually stopped, particularly in patients with weekly regimens that put them at higher risk of corticosteroid toxicity. Premedication is also recommended before intraperitoneal infusions of both docetaxel and paclitaxel.

### Mechanisms of HSRs

Uncertainty remains regarding the mechanisms through which taxanes cause HSRs. Most reactions seem to depend on the drug solvents, Cremophor EL and polysorbate 80, which cause a nonspecific mast cell and basophil degranulation secondary to complement activation. However, some data suggest that the taxane moiety itself can also cause a nonspecific basophil degranulation, and at least one case of IgE-mediated hypersensitivity to paclitaxel has been reported. Interestingly, nanoparticle-bound paclitaxel (nab-paclitaxel) is a newer formulation of the drug that is exempt of solvent and can be infused over 30 minutes without premedication. Its use in several clinical trials and in a few patients who had a prior reaction to paclitaxel has not been associated with HSRs, likely implicating Cremophol EL as the culprit of most HSRs to paclitaxel. Postmarketing surveillance has identified rare cases of HSRs (including anaphylaxis) to nab-paclitaxel. Therefore, caution should also be exercised when using this agent in patients who had a previous taxane HSR, because some may be reactive to the taxane moiety.

### Management of HSRs

HSRs to taxanes should be managed as shown in Figure 2 in accordance with the NCCN Guidelines for Ovarian Cancer (to view the most recent version of these guidelines, visit NCCN.org). When an HSR occurs, the infusion should be stopped immediately and the reaction treated as outlined earlier for acute management of HSRs. Several studies show that rapid re-treatment after resolution of the HSR is successful in most patients.
(93% in a study by Markman et al\textsuperscript{67}) with added steroids (dexamethasone, hydrocortisone) and a slower infusion rate of up to 24 hours.\textsuperscript{2,7,49,68} However, this approach is not uniformly successful and HSRs recur in some patients despite all precautions.\textsuperscript{17,67,68,70,89,90} Alternatively, or if rechallenge fails, consideration can be given to switching from paclitaxel to docetaxel or vice versa, although few data exist supporting this practice.\textsuperscript{2}

In a cohort of 10 patients, Dizon et al\textsuperscript{91} found that 90% of patients reacted to paclitaxel and then to docetaxel. More recently, Sanchez-Munoz et al\textsuperscript{92} showed that the cross-reactivity rate from paclitaxel to docetaxel was 38%, and that from docetaxel to paclitaxel was 44%, showing the limited utility of this approach.\textsuperscript{92}

In patients with a severe or life-threatening HSR, rechallenge or switching from one taxane to another is not recommended because of the potential harm that might be caused to the patient in the event of a recurrent HSR.\textsuperscript{2} Although not validated, skin testing may be a useful tool in the future to identify patients with an IgE-mediated allergy to paclitaxel or docetaxel in whom rechallenge may be unwarranted.\textsuperscript{27,51,84} If the patient is likely to benefit from taxane treatment and no equally effective alternative agent can be used, the taxane could be readministered through a desensitization protocol.\textsuperscript{2,7,49,68} Different desensitization protocols have been used for paclitaxel and, to a lesser extent, docetaxel administration, with an excellent record regarding safety and efficacy.\textsuperscript{7,17,27,49,51,66–68,91} From 2000 to 2006, 60 patients underwent 331 intravenous and 12 intraperitoneal desensitizations to paclitaxel using the same protocol as the one used for platinum drugs (Table 4).\textsuperscript{7,49,68} Breakthrough reactions occurred in 9.3% of patients during the desensitization procedures and were all less severe than the initial HSR, and none led to the discontinuation of therapy.\textsuperscript{7,21} Desensitization protocols used for platinum drugs should be performed by allergists or specialists with expertise in desensitization procedures, and patients in whom desensitization is considered should be preferably referred to an academic center with this expertise.\textsuperscript{2}

### Other Drugs Used in Ovarian Cancer

#### Pegylated Liposomal Doxorubicin

The incidence of HSRs to PLD averages 8% and is observed in up to 25% in some series.\textsuperscript{91} The clinical picture and the mechanism of reactions to PLD are similar to those of taxanes.\textsuperscript{93} Reactions usually occur during the first cycle of the drug, and signs and symptoms are compatible with mast cell degranulation.\textsuperscript{7,93,94} Complement activation has been shown to occur in vivo in patients being infused with PLD, and is thought to be responsible for mast cell activation.\textsuperscript{93} Interestingly, the free form of doxorubicin does not cause HSRs, thus making pegylated liposomes the likely trigger for those reactions.\textsuperscript{93} HSRs to PLD are usually managed in a similar manner to HSRs to taxanes, as shown in Figure 2.\textsuperscript{2} Mild reactions usually resolve after stopping the infusion and administering antihistamines.\textsuperscript{93} The infusion can then generally be resumed safely at a slower rate.\textsuperscript{91} However, patients with recurrent and severe and life-threatening HSRs to PLD should not be rechallenged, and might be referred to an allergist or a specialist in desensitization for evaluation if continued treatment with PLD is judged beneficial.\textsuperscript{2,7} Skin testing cannot be performed because of the vesicant properties of the drug, but desensitization procedures have been performed successfully in 6 patients.\textsuperscript{7,49}

#### Etoposide

HSRs to etoposide usually occur during the initial minutes of the first infusion, with features of mast cell activation, and like with docetaxel, have been attributed to its solvent polysorbate 80.\textsuperscript{95–97} The incidence is estimated to be between 1% and 3%, and reactions are usually mild and may be prevented by premedication with corticosteroids and antihistamines in some patients.\textsuperscript{95,97} The oral formulation, etoposide phosphate without polysorbate 80, has been used successfully in several patients who had HSRs to etoposide.\textsuperscript{95–103} However, at least 2 patients have been reported to react to etoposide phosphate in a phase I trial, and a case of anaphylaxis to etoposide phosphate after an HSR to etoposide was recently reported.\textsuperscript{96,103}

#### Gemcitabine and Bevacizumab

HSRs to gemcitabine have rarely been described, although desensitization procedures have been performed successfully in some patients (M. Castells, MD, PhD; U. Govindarajulu, PhD, MS; D. Sloane, MD; unpublished data, February 27, 2014.).\textsuperscript{104} Bevacizumab is a humanized recombinant monoclonal antibody targeting vascular endothelial growth factor-A (VEGF-A), which has recently been used as an adjunct to first-line therapy in women with ovarian cancer.\textsuperscript{2} In contrast to other monoclonal antibodies, reactions with features of cytokine release seem
to be uncommon with bevacizumab. However, IgE-mediated reactions have occurred, supported by a positive skin test, and desensitization procedures have been successfully performed (M. Castells, MD, PhD; U. Govindarajulu, PhD, MS; D. Sloane, MD; unpublished data, February 27, 2014.).

**Granisetron, Ondansetron, and Corticosteroids**

Although rarely incriminated in HSRs occurring during or shortly after the administration of a chemotherapeutic drug, granisetron, ondansetron, and corticosteroids have also been deemed responsible for those reactions in several patients. In at least one case, the patient experienced urticaria 20 minutes into his seventh oxaliplatin infusion, mimicking an oxaliplatin allergy. This possibility should be kept in mind when evaluating patients with HSRs during or shortly after a chemotherapy infusion.

**Conclusions**

The management of HSRs to chemotherapy in patients with ovarian cancer is complex, requiring knowledge of the mechanisms behind those reactions and of the different management options, ranging from drug reintroduction to discontinuation. Several tools can assist the clinician in this difficult decision-making process. For instance, an elevated serum tryptase level following an acute reaction can confirm mast cell involvement in the HSR, emphasizing the need for prudence if reintroduction is attempted. And in evaluating a patient after an HSR, skin testing can accurately identify patients with an allergy to platinum drugs, in whom reintroduction should only be considered through a desensitization protocol. In the future, skin testing to other drugs, including taxanes, may also prove helpful.

Recently, the development of desensitization protocols with remarkable safety records has allowed patients with ovarian cancer who experienced mast cell–mediated chemotherapy HSRs of any severity to be re-treated with these life-saving molecules. Experience with these protocols is increasing rapidly, because their usefulness in the management of chemotherapy HSRs is being increasingly recognized. Efforts are now needed to increase awareness about desensitization procedures so that more patients may benefit. This is a challenge that will require the close collaboration of patients, nurses, oncologists, and allergists.

**References**

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