Incidences of Hypersensitivity Reactions to Carboplatin or Paclitaxel in Patients With Ovarian, Fallopian Tube, or Primary Peritoneal Cancer With or Without BRCA1 or BRCA2 Mutations

ANDREW GARCIA,1 PharmD, COREY FRAHM,1 PharmD, JOANNE M. JETER,2 MD, IVO ABRAHAM,3 PhD, RN, SETSUKO K. CHAMBERS,3 MD, JANIEL M. CRAGUN,3 MD, and ALI McBRIDE,1 PharmD

Abstract
The association of BRCA mutation status with hypersensitivity reactions (HSRs) to carboplatin has gained interest in recent years, particularly in patients with ovarian, fallopian tube, and primary peritoneal cancer. The primary objective of this study is to determine whether the presence of BRCA mutations increased the likelihood of HSRs to carboplatin. The incidence of HSRs to paclitaxel and symptom grade based on the Common Terminology Criteria for Adverse Events, version 4.0, were explored as secondary endpoints. A retrospective chart review of patients with ovarian, fallopian tube, or primary peritoneal cancer at the University of Arizona Cancer Center who underwent treatment with carboplatin-containing regimens and received genetic testing was performed. Institutional review board approval was obtained for this study. Fisher’s exact test was used to analyze the primary outcome. Out of 167 initial patients, 62 with germline test results constituted the evaluable sample. 15 of 62 (24.2%) BRCA-tested patients were treated with carboplatin monotherapy, while 44 of 62 (71.0%) patients were treated with paclitaxel-containing regimens. Hypersensitivity reactions occurred in 4 of 13 (30.8%) BRCA-mutated patients and 22 of 49 (44.9%) BRCA wild-type patients (p = .5291). Hypersensitivity reactions to paclitaxel occurred in 1 of 13 (7.7%) BRCA-mutated patients and 26 of 49 (53.1%) BRCA wild-type patients (p = .0039). Overall, there were 11 grade 1 reactions, 14 grade 2 reactions, and 16 grade 3 reactions to carboplatin. All reactions to carboplatin in BRCA-
Mutated patients were grade 1. All paclitaxel reactions manifested as grade 2. The sample size was the main study limitation. The presence of BRCA mutations was not statistically significantly associated with a higher incidence of HSRs to carboplatin, but was statistically significant with regards to paclitaxel.

Many antineoplastic agents have been known to cause hypersensitivity reactions (HSRs). The incidences of HSRs are highly variable within and between all major categories of antineoplastic drugs (DeMoor et al., 2011). Of the platinum compounds, carboplatin has been reported to account for 0.73% of all reactions from infused chemotherapies, and up to 50% of all reactions in platinum-based chemotherapies (DeMoor et al., 2011). Earlier literature has cited cisplatin and carboplatin as the cause of a wide range of HSRs in 10% to 27% of patients receiving these agents, generally occurring after 4 to 6 cycles of treatment (Markman et al., 1999; Zanotti & Markman, 2001). Hypersensitivity reactions generally involve signs and symptoms ranging from mild skin reactions to more severe reactions such as respiratory arrest and death.

Reports of HSRs to carboplatin have increased in recent years, with an estimated incidence of 8% to 16% when used in the first-line setting, and as high as 44% when used in the second- and third-line settings (Moon et al., 2013). Patients with deleterious germline BRCA1 or BRCA2 mutations may be more likely to receive multiple cycles of platinum-based chemotherapy due to increased therapeutic susceptibility with such mutations, and thus may be more likely to develop HSRs as a result of higher cumulative exposure (Alsop et al., 2012). In a previous study on the association of BRCA mutations and HSRs to carboplatin, Moon and colleagues found that 23 of 29 (79.3%) patients with any history of HSRs to carboplatin had a deleterious BRCA1 or BRCA2 mutation and had a higher incidence and severity of HSRs to carboplatin compared to 29 of 58 (50%) in a control group of BRCA wild-type patients (Moon et al., 2013). This is one of the few studies that has addressed the possible association of BRCA mutations with the development of HSRs to carboplatin.

In light of the study by Moon and colleagues, as well as further studies and case reports investigating potential relationships between BRCA mutations and carboplatin, we further explored the possible association between HSR development and BRCA1/BRCA2 mutation status in an initial sample of 167 patients with ovarian, fallopian tube, or primary peritoneal cancer receiving carboplatin-based therapy at the University of Arizona Cancer Center.

**METHODS**

**Study Design**

This study was a retrospective chart review. The inclusion criteria involved diagnosis of ovarian, fallopian tube, or primary peritoneal cancer in patients who had received at least one treatment with carboplatin, definitive testing for BRCA mutation status, a nontreatment period of at least 6 months from prior platinum therapy, adequate end-organ function, and measurable or evaluable disease. We started with a review of the charts for 167 patients who had received carboplatin, been diagnosed with ovarian, fallopian tube, or primary peritoneal cancer, and were receiving treatment with carboplatin at our site between January 2012 and April 2016 (Figure 1). Of this initial sample, 62 had received definitive testing for BRCA mutations and constituted the evaluable sample. The study was approved and monitored by the University of Arizona institutional review board committee as well as the University of Arizona Cancer Center scientific review committee.

Demographic variables included age, comorbid conditions, primary cancer diagnosis, cancer stage, recorded history of allergy to medications, environmental factors or food allergies (see Appendix A), previous chemotherapy, prior platinum regimens and platinum cycles, as well as premedications and outpatient medications that may have impacted the development of a reaction (steroids, H1/H2-receptor antagonists, and proton pump inhibitors). The University of Arizona Cancer Center’s standard prophylaxis regimen for patients undergoing a combination chemotherapy regimen consisted of IV palonosetron at 0.25 mg/dexamethasone at 20 mg, oral diphenhydramine at 50 mg, and oral
famotidine at 20 mg, all given 30 minutes prior to infusion. For single-agent carboplatin regimens, premedication therapy was IV palonosetron at 0.25 mg/dexamethasone at 10 mg, IV diphenhydramine at 25 mg, and IV famotidine at 25 mg.

The Common Terminology Criteria for Adverse Events (CTCAE version 4.0, general disorders and administration site conditions) was used to determine reaction severity. Reactions were categorized as grade 1 if the reaction was only mild and transient, infusion interruption was not indicated, or an intervention was not indicated. Reactions were categorized as grade 2 if intervention or infusion interruption were indicated, but the patient responded promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids), or if prophylactic medications were indicated for less than 24 hours. Reactions were categorized as grade 3 if they were prolonged (not rapidly responsive to symptomatic medication and/or brief interruption of infusion), symptoms recurred following initial improvement, or if hospitalization was indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grades 4 and 5 reactions were categorized as those leading to life-threatening consequences or if urgent intervention was indicated, and death, respectively.

The primary endpoint included the incidence of HSRs in patients with and without germline BRCA mutations receiving carboplatin treatment for ovarian, primary peritoneal, or fallopian tube malignancy. Secondary endpoints included cumulative platinum dose, cumulative number of prior platinum cycles, grade of HSRs, symptoms experienced during the infusion reaction (e.g., itchiness, rash, etc.), and treatment outcome (successful completion of therapy or discontinuation of treatment due to adverse effect or progression of disease). Cumulative doses and platinum cycles for patients were collected to observe differences between groups in cumulative platinum chemotherapy received before experiencing reactions. During the study, the protocol was amended to allow the collection of HSR data in paclitaxel-treated patients as an exploratory secondary endpoint to see whether higher rates of hypersensitivity occurred with this drug as well, given its common use in combination therapy with carboplatin.

Data were entered into Excel spreadsheets for analysis, with statistical analysis conducted through Excel and Prism 7 software. Data were stored on a secure server with password access at the cancer center, with only the investigators having access to the data files.

Statistical Analysis
Descriptive and clinical variables were analyzed by calculating medians and standard deviations for continuous variables (age, weight, height), as well as frequencies, and percentages for categorical variables (gender, germline BRCA mutation status, comorbid conditions, history of allergy, severity grade, symptoms, and treatment outcome). Fisher’s exact test was used to analyze the primary endpoint of carboplatin HSRs between groups and the secondary endpoint of paclitaxel HSRs between groups. The a priori $\alpha$ level was set at 0.05.

RESULTS
Patient Enrollment and Characteristics
In total, 62 patients (13 BRCA mutated, 49 BRCA wild type) were evaluated after satisfying appropriate inclusion and exclusion criteria. Baseline characteristics for patients evaluated in the study are reported in Table 1. Of the 13 patients found to have germline BRCA mutations, 9 tested positive for BRCA1, while 4 tested positive for BRCA2.

The overall incidence of HSRs to carboplatin in patients with deleterious BRCA mutations was not increased significantly with respect to that observed in wild-type BRCA patients (4 of 13 [30.8%] vs. 22 of 49 [44.9%], respectively; $p =$
Table 1. Patient Characteristics (N = 62)

|                                | BRCA wild-type  | BRCA mutated  |
|--------------------------------|-----------------|---------------|
|                                | (n = 49)        | (n = 13; BRCA1 = 9; BRCA2 = 4) |
| Age, median (SD)               | 67 (11.0)       | 59 (13.0)     |
| Height (cm), median (SD)       | 163 (2.6)       | 160 (4.3)     |
| Weight (kg), median (SD)       | 69 (18.2)       | 67.2 (15.2)   |
| History of allergy, no. (%)   | 38 (77.6%)      | 1 (84.6%)     |
| Previous chemotherapy, no. (%)| 16 (32.7%)      | 8 (61.5%)     |
| Prior platinum treatment, no. (%)| 12 (24.5%) | 7 (53.8%)     |
| Number of prior platinum cycles, no. (%) |             |              |
| 0                              | 39 (0)          | 6 (0)         |
| 1-5                            | 3 (2.3)         | 2 (0)         |
| 6 or more                      | 7 (1.1)         | 5 (4.4)       |
| Prior HSRs to chemotherapy, no. (%)| 5 (10.2%) | 1 (7.7%)      |
| Race/ethnicity, no. (%)        |                 |               |
| Caucasian                      | 34 (69.4%)      | 8 (61.5%)     |
| Hispanic                       | 6 (12.2%)       | 4 (3.1%)      |
| Native American                | 1 (2.0%)        | 0 (0.0%)      |
| Other/mixeda                   | 8 (16.3%)       | 1 (7.7%)      |
| Major comorbidities, no. (%)   |                 |               |
| Hypertension                   | 20 (40.8%)      | 3 (23.1%)     |
| Type 2 diabetes                | 6 (12.2%)       | 2 (15.4%)     |
| Depression                     | 13 (26.5%)      | 2 (15.4%)     |
| Osteoarthritis                 | 13 (26.5%)      | 1 (7.7%)      |
| GERD                           | 14 (28.6%)      | 1 (7.7%)      |
| Hypothyroidism                 | 16 (32.7%)      | 3 (23.1%)     |
| Cancer diagnosis, no. (%)      |                 |               |
| Ovarian                        | 43 (87.8%)      | 12 (92.3%)    |
| Primary peritoneal             | 5 (10.2%)       | 0 (0.0%)      |
| Fallopian tube                 | 1 (2.0%)        | 1 (7.7%)      |
| Oncologic stage at diagnosis, no. (%) |         |               |
| Stage I                        | 3 (6.1%)        | 0 (0.0%)      |
| Stage II                       | 3 (6.1%)        | 1 (7.7%)      |
| Stage III                      | 20 (40.8%)      | 8 (61.5%)     |
| Stage IV                       | 15 (30.6%)      | 3 (23.1%)     |
| Unstaged                       | 8 (16.3%)       | 1 (7.7%)      |
| Treatment outcome, no. (%)     |                 |               |
| Successful completion          | 29 (59.2%)      | 7 (53.8%)     |
| Ongoing at time of data cutoff | 10 (20.4%)      | 4 (30.8%)     |
| Discontinuationb               | 8 (16.3%)       | 2 (15.4%)     |
| Changed chemotherapy           | 2 (4.1%)        | 0 (0.0%)      |

Note. SD = standard deviation; GERD = gastroesophageal reflux disease.

aOther mixed: BRCA wild type: Caucasian/Native American (n = 1), Caucasian/Hispanic (n = 3), Black/Hispanic, (n = 1), other (n = 2), and Hispanic/other (n = 1); BRCA mutated: Hispanic/other (n = 1).
bReasons included decision to stop further therapy due to disease progression (n = 7), adverse reaction to carboplatin (n = 1), lack of follow-up (n = 1), or transfer of care to another institution (n = 1).
.5291), which is shown in Table 2. There was a statistically significant difference noted in the incidence of paclitaxel HSRs in BRCA-mutated patients vs. that found in BRCA wild-type patients (1/13 [7.7%] BRCA-mutated patients vs. 26 of 49 [53.1%] BRCA wild-type patients; p = .0039). Additionally, 3 of 4 (75%) BRCA-mutated patients who had reactions had not had prior chemotherapy, while 13 of 22 (59.1%) BRCA wild-type patients had not had prior chemotherapy. The average cumulative carboplatin dose for all patients who had a reaction was found to be 3,113 mg based on the cumulative lifetime dose received up to the point of the reaction. BRCA-mutated patients received an average cumulative dose of 2,883 mg, while BRCA wild-type patients had an average cumulative dose of 3,155 mg.

The total number of carboplatin cycles received prior to carboplatin reaction was compared between BRCA-mutated patients and BRCA wild-type patients, as reported in Figure 2. This includes any previous cycles documented in the patients’ charts as well as those they received during the study period. Hypersensitivity reactions were documented within the range of 2 to 12 cycles across the study groups.

**Adverse Events**

Overall, the carboplatin infusion reactions included 11 grade 1 reactions, 14 grade 2 reactions, and 16 grade 3 reactions. All reactions in BRCA-mutated patients manifested as grade 1 reactions (red skin, desquamation, edema, and itching eyes), while the rest of the reactions manifested in BRCA wild-type patients. Most BRCA wild-type patients developing HSRs presented with more than one symptom, and the symptoms were often grade 2 or 3, as shown in Table 3. Reactions were categorized as grade 3 largely because infusion was interrupted rather than hospitalization due to clinical sequelae. In the paclitaxel group, the most common symptom observed was flushing. These reactions all manifested as grade 2 infusion reactions, requiring use of appropriate supportive therapies as described in the methods section. No grade 4 or grade 5 reactions were identified in our study.

**DISCUSSION**

With platinum compounds gaining more widespread use for various malignancies, effective pharmacovigilance for detecting adverse effects is paramount. Many health systems currently use institution-specific hypersensitivity protocols based on current standards of care, but studies continue to evaluate the potential association of BRCA mutations with adverse reactions to chemotherapy regimens. These studies are especially important for platinum therapies, since patients with gynecologic malignancies and deleterious BRCA mutations have been shown to respond particularly well to platinum-based regimens in the gynecologic malignancy literature (Matulonis et al., 2016). Patients being treated for cancers that are particularly susceptible to platinum agents,

| Table 2. Development of Hypersensitivity Reactions |
|-----------------------------------------------|
| **Documented HSRs to carboplatin**             |
| BRCA mutated (n = 13; BRCA1 = 9; BRCA2 = 4)   |
| HSR occurred                                  |
| 4/13 (30.8%)                                  |
| No HSR occurred                               |
| 9/13 (69.2%)                                  |
| p value                                       |
| .5291                                         |
| BRCA wild-type (n = 49)                       |
| 22/49 (44.9%)                                 |
| 27/49 (55.1%)                                 |

| **Documented HSRs to paclitaxel**               |
| BRCA mutated (n = 13; BRCA1 = 9; BRCA2 = 4)   |
| HSR occurred                                  |
| 1/13 (7.7%)                                   |
| No HSR occurred                               |
| 12/13 (92.3%)                                 |
| p value                                       |
| .0039                                         |
| BRCA wild-type (n = 49)                       |
| 26/49 (53.1%)                                 |
| 23/49 (46.9%)                                 |

| **Average cumulative dose of carboplatin for patients who had reaction** |
|-----------------------------|
| BRCA mutant (n = 4)         | 2,883 mg |
| BRCA wild-type (n = 22)     | 3,155 mg |
| Total (n = 26)              | 3,113 mg |

**Note.** Development of HSRs in study using Fisher’s exact test. HSR = hypersensitivity reaction.

*3/4 BRCA-mutated patients had not had prior chemotherapy.

*13/22 BRCA wild-type patients had not had prior chemotherapy.
such as BRCA-deficient ovarian cancer, may be more likely to receive a higher cumulative lifetime dose of carboplatin during their treatment based on sensitivity to carboplatin therapy. This susceptibility is related to the loss of function of mismatch repair proteins normally coded for by BRCA, which makes it more challenging for afflicted cells to repair damage caused by intercalation of DNA as a result of carboplatin’s mechanism of action (Miki et al., 1994). However, consistent exposure to platinum is thought to be associated with a greater likelihood of developing infusion reactions as a result of sensitization to the drug.

A causal relationship between BRCA mutations and HSRs to chemotherapy classes has yet to be established at this time. Previous research has shown conflicting results. In one study, patients with a family history of a deleterious BRCA mutation did not differ in their rates of hospitalizations or emergency department visits when curative chemotherapy was used in either BRCA-deficient or BRCA wild-type patients (Egloff & Jatoi, 2016).
Table 3. Hypersensitivity Symptoms for Carboplatin and Paclitaxel

| Carboblatin hypersensitivity symptoms | BRCA wild-type | BRCA mutated |
|--------------------------------------|----------------|--------------|
| Grade of reaction                    |                |              |
| Grade 1                              | 7              | 4            |
| Grade 2                              | 8              | 0            |
| Grade 3                              | 7              | 0            |
| Manifestation*                       | Grade 1 | Grade 2 | Grade 3 |
| Itching body                         | 4          | 3          | 2       |
| Rash                                 | 3          | 2          | 1       |
| Desquamation                         | 2          | 1          | 0       |
| Flushing                             | 1          | 3          | 3       |
| Edema                                | 1          | 0          | 1       |
| Hives                                | 0          | 1          | 1       |
| Chest pain                           | 0          | 3          | 3       |
| Cough                                | 0          | 1          | 0       |
| Tickle in throat                     | 0          | 1          | 0       |
| Stinging                             | 0          | 0          | 1       |
| Abdominal pain                       | 0          | 0          | 1       |
| Shortness of breath                  | 0          | 0          | 2       |
| Swollen tongue                       | 0          | 0          | 1       |

| Paclitaxel hypersensitivity symptoms | BRCA wild-type | BRCA mutated |
|--------------------------------------|----------------|--------------|
| Grade of reaction                    |                |              |
| Grade 1                              | 0              | 0            |
| Grade 2                              | 26             | 1            |
| Grade 3                              | 0              | 0            |
| Manifestation*                       | Grade 1 | Grade 2 | Grade 3 |
| Itching throat                       | 0          | 6          | 0       |
| Itching body                         | 0          | 6          | 0       |
| Flushing                             | 0          | 10         | 0       |
| Dyspnea on exertion                  | 0          | 1          | 0       |
| Shortness of breath                  | 0          | 7          | 0       |
| Hives                                | 0          | 3          | 0       |
| Burning                              | 0          | 1          | 0       |
| Chest pain                           | 0          | 6          | 0       |
| Abdominal pain                       | 0          | 2          | 0       |

Note. *Manifestation refers to symptoms occurring during hypersensitivity episode; grade reflects outcome based on CTCAE v4.0, general disorders and administration site conditions.

*All paclitaxel reactions were grade 2 (therapy or infusion interruption requiring prompt symptomatic treatment [e.g., antihistamines] for less than 24 hours).
Similarly, accounts in the breast cancer literature reported no difference in acute toxicities to anthracyclines or taxanes in the neoadjuvant setting in patients presenting with BRCA mutations as compared to those without identified BRCA germline mutations (Drooger et al., 2016; Huszno, Budryk, Kołosza, & Nowara, 2013). Such findings differ from those of Moon and colleagues, who reported a difference in HSRs to carboplatin for patients previously identified as having BRCA-mutated status.

With regards to the likelihood of developing a reaction, previous studies indicate that HSRs occur in less than 1% of patients in carboplatin cycles 1 to 5 and 6.5% of patients in cycle 6. However, in cycles 7 and greater, up to 27% of patients may experience a reaction, and up to 44% may experience reactions in the third-line retreatment setting (Hoekstra, Hurteau, Kirschner, & Rodriguez, 2009; Makrilia, Syrigou, Kaklamanos, Manolopoulos, & Saif, 2010). These reactions are thought to be due to an immunoglobulin E (IgE)-mediated mechanism (Iwamoto et al., 2014). The mildest manifestations include skin rashes, urticaria, flushing, palmar itching, burning, edema of the face and hands, abdominal cramping and diarrhea, back pain, and pruritus, and usually resolve quickly with antihistamines and steroids.

The more severe grade 3 and 4 reactions such as bronchospasm, tachycardia, hypotension or hypertension, seizures, and chest pain are often seen after the sixth infusion cycle, although these manifestations have been estimated to occur in only 1.6% of patients who experience hypersensitivity (Makrilia et al., 2010).

Risk factors for platinum HSRs should always be reviewed prior to the beginning of therapy, focusing on factors such as female gender, age, history of allergy to medication and environmental triggers, environmental exposure to platinum-containing chemicals, a platinum-free interval greater than 13 months, single maximal doses greater than 650 mg, and a cumulative carboplatin exposure of 8,000 mg or more (Gadducci et al., 2008; Makrilia et al., 2010; Markman et al., 1999; Navo et al., 2006; O’Cearbhaill et al., 2010; Schwartz et al., 2007). Some studies have evaluated whether the incidence of carboplatin HSRs is higher in gynecologic malignancies than in other malignancies, but have not found a statistically significant difference in risk based on carboplatin administration alone (Navo et al., 2006).

Combination therapy has also been considered as an associated risk factor for HSRs. Carboplatin in combination with paclitaxel remains the standard front-line treatment for stage IC, II, III, and IV primary ovarian, fallopian tube, and peritoneal carcinomas following cytoreductive surgery or in the neoadjuvant setting (Matulonis et al., 2016; Moon et al., 2013). Carboplatin is also the preferred agent in combination regimens for platinum-sensitive disease. Several studies have demonstrated the efficacy of carboplatin in both single-agent and combination treatment for initial management of platinum-sensitive disease with drugs such as paclitaxel, docetaxel, bevacizumab, and liposomal doxorubicin (Bell et al., 2006; Katsumata et al., 2009, 2013; Ozols et al., 2003; Pignata et al., 2014; Vasey et al., 2004), although the benefit on progression-free survival of dose-dense weekly paclitaxel and carboplatin is still unclear (Chan et al., 2016).

Most of our patients experienced reactions between 4 and 6 total cycles of treatment, with cycle 4 being the most common for both BRCA-mutated and BRCA wild-type patients. This finding differs from the previously reported data indicating that reactions occur most commonly after 6 to 8 cycles of treatment (Hoekstra et al., 2009; Makrilia et al., 2010). Over half of the patients who had a reaction and who were BRCA mutated had not received prior chemotherapy, but had received combination chemotherapy, which may be related to exposure to two different chemotherapies with HSR potential. However, given the small sample size, this warrants further investigation in future studies. A recent poster presentation by Altweger and colleagues reported a strong association between carboplatin HSRs and BRCA deficiency in ovarian cancer patients, highlighting a possible link between carboplatin-induced DNA damage, the immune system, and HSRs (Altweger, 2017, Altweger et al., 2017). A single-center study by Maccaroni and colleagues reported higher rates of HSRs to platinum-based compounds in BRCA-mutated patients compared to BRCA wild-type patients (64% vs. 8%), although whether the agent in...
question was carboplatin was not reported (Maccaroni et al., 2016). However, a 2016 study by Jerzak and colleagues focusing on prevention of hypersensitivity reactions in ovarian cancer patients found that BRCA mutation status was not predictive of developing a reaction (Jerzak et al., 2016). Their sample included 37 patients with BRCA1/BRCA2 mutations and 84 BRCA wild-type patients. All had epithelial ovarian cancer and had received greater than 6 cycles of carboplatin chemotherapy. These findings underscore the importance of future research in ascertaining the association between BRCA status and carboplatin HSRs to resolve the lack of consensus that exists today.

As stated before, we did not observe a difference in HSRs with respect to carboplatin in BRCA-mutated vs. BRCA wild-type patients; however, we did observe a statistically significant difference in the incidence of paclitaxel HSRs. Consistent with previous studies in which paclitaxel reactions most commonly manifested earlier during treatment, most of our patients who developed a reaction did so after the first cycle (16/27 [59.2%]; 15 BRCA wild-type patients, 1 BRCA-mutated patient). However, it should be noted that this was an exploratory aim, as only one patient with a BRCA mutation developed a reaction to paclitaxel. Furthermore, the reaction to paclitaxel may have been related to the solubilizing agent cremophor rather than the drug itself.

The symptoms and grades of hypersensitivity reactions observed in our study were similar to those previously reported in the literature, with rash and pruritus as the most common adverse events. It is worth noting that all patients who developed grade 3 reactions were classified as having such mainly based on prolonged reactions or recurrence of symptoms following initial improvement, rather than hospitalization for clinical sequelae.

Paclitaxel HSRs occurred in 26 of 49 (53.1%) BRCA wild-type patients and 1 of 13 (7.7%) BRCA-deficient patients. Rates of paclitaxel HSRs in the literature suggest that roughly 10% of premedicated patients will develop a reaction immediately, with 10% of these patients subsequently developing severe reactions, which differed from 53.1% of patients who experienced HSRs in our study (Picard & Castells, 2015). These findings emphasize the importance of continued research in this area, not just with carboplatin, but with all chemotherapy agents that patients may receive during their course of care.

LIMITATIONS
Limitations of our study include the retrospective design, the relatively small sample size, ongoing infusions at the time of data censoring, lack of BRCA testing in a larger number of patients than we had originally expected (64 excluded from original sample due to lack of BRCA testing), and possibility of reaction to the paclitaxel solubilizer agent rather than the drug itself. Reasons for not testing BRCA at that time are not documented but may be due to low suspicion that these patients’ cancer development was influenced by a BRCA mutation and/or the lack of high-grade serous histology, although germline BRCA testing for all histologic subtypes of epithelial ovarian cancer is now considered standard of care according to the latest National Comprehensive Cancer Network Guidelines for ovarian cancer (Matulonis et al., 2016; U.S. Food & Drug Administration, 2016).

CONCLUSIONS
As carboplatin continues to be a major front-line treatment for ovarian, fallopian tube, and primary peritoneal cancer, it is paramount to monitor and try to predict whether patients will have an increased likelihood of HSRs based on risk factors such as genetics. Additional research is warranted to better characterize this association with carboplatin HSRs. A meta-analysis would be beneficial to address conflicting results arising in the literature thus far. Due to the relatively rare nature of severe reactions, future studies would be best conducted in a large patient population for more accurate and precise risk assessment. Furthermore, since it is difficult to say with certainty whether the sole reaction to paclitaxel in the BRCA-mutated group was due to the drug itself, it may be beneficial in further studies to investigate such a reaction with formulations less likely to mask true hypersensitivity to the agent in question.

Authors’ Note
This work was previously presented as a poster at the Hematology/Oncology Pharmacy Association...
tion on March 30, 2017, and the abstract appeared in the e-publication for the American Society of Clinical Oncology’s Annual Meeting in June 2018.

Disclosure
The authors have no conflicts of interest to disclose.

References
Alspot, K., Fereday, S., Meldrum, C., deFazio, A., Emmanuel, C., George, J., Mitchell, G. (2012). BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: A report from the Australian ovarian cancer study group. Journal of Clinical Oncology, 30(21), 2654–2663. https://doi.org/10.1200/JCO.2011.39.8545

Alwarger, G. H. (2017). Carboplatin hypersensitivity linked to BRCA deficiency in ovarian cancer. Retrieved from http://www.onlive.com/conference-coverage/sgo-2017/carboplatin-hypersensitivity-linked-to-brca-deficiency-in-ovarian-cancer

Alwarger, G., Gressel, G. M., English, D. P., Nelson, W. K., Carrillo, N., Silva, D.-A., Ratner, E. S. (2017). Platinum desensitization in patients with carboplatin hypersensitivity: A single-institution retrospective study. Gynecologic Oncology, 144(1), 77–82. https://doi.org/10.1016/j.ygyno.2016.09.027

Bell, J., Brady, M. F., Young, R. C., Lage, J., Walker, J. L., Look, K. Y., Spirtos, N. M. (2006). Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group study. Gynecologic Oncology, 102(3), 432–439. https://doi.org/10.1016/j.ygyno.2006.06.013

Chan, K. J., Brady, M. F., Pensom, R. T., Huang, B., Birrer, M. J., Walker, J. L., Monk, B. J. (2016). Weekly vs. every 3-week paclitaxel and carboplatin for ovarian cancer. New England Journal of Medicine, 374(8), 738–748. https://doi.org/10.1056/NEJMoa1505067

DeMoor, P. A., Matusov, Y., Kelly, C., Kolan, S., Barnachea, L., & Bazhenova, L. (2011). A retrospective review of the frequency and nature of acute hypersensitivity reactions at a medium-sized infusion center: Comparison to reported values and inconsistencies found in literature. Journal of Cancer, 2(1), 153–164. https://doi.org/10.7150/jca.2.153

Drooger, J. C., Heemskerk-Gerritsen, B. A. M., Smollenbroek, N., Epskamp, C., Seynaeve, C. M., & Jager, A. (2016). Toxicity of (neo)adjuvant chemotherapy for BRCA1- and BRCA2-associated breast cancer. Breast Cancer Research and Treatment, 156(3), 557–566. https://doi.org/10.1007/s10549-016-3777-0

Egloff, H., & Jatoi, A. (2016). Do ovarian cancer patients with a family history of cancer (suspected BRCA1 or BRCA2 mutation) suffer greater chemotherapy toxicity? Cancer Investigation, 34(10), 531–535. https://doi.org/10.1080/07357907.2016.1242011

Gadducci, A., Tana, R., Tetì, G., Zanca, G., Fanucchi, A., & Genazzani, A. R. (2008). Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. International Journal of Gynaecological Cancer, 18(4), 615–620. https://doi.org/10.1111/j.1525-1438.200701063.x

Hoekstra, A. V., Hurteau, J. A., Kirschner, C. V., & Rodriguez, G. C. (2009). The combination of monthly carboplatin and weekly paclitaxel is highly active for the treatment of recurrent ovarian cancer. Gynecologic Oncology, 115(3), 377–381. https://doi.org/10.1016/j.ygyno.2009.08.021

Huszno, J., Budryk, M., Kołosza, Z., & Nowara, E. (2013). The influence of BRCA1/BRCA2 mutations on toxicity related to chemotherapy and radiotherapy in early breast cancer patients. Oncology, 85(5), 278–282. https://doi.org/10.1159/000345834

Iwamoto, T., Hirai, H., Yamaguchi, N., Kobayashi, N., Sugimoto, H., Tahata, T., & Okuda, M. (2014). Carboplatin-induced severe hypersensitivity reaction: Role of IgE-dependent basophil activation and FceRI. Cancer Science, 105(11), 1472–1479. https://doi.org/10.1111/cas.12538

Jerzak, K. J., Deghan Manshadi, S., Ng, P., Maganti, M., McCuaig, J. M., Bulter, M., Mackay, H. J. (2016). Prevention of carboplatin-induced hypersensitivity reactions in women with ovarian cancer. Journal of Oncology Pharmacy Practice, 24(2), 83–90. https://doi.org/10.1007/s11786-016-09028

Katsumata, N., Yasuda, M., Isonishi, S., Takahashi, F., Michimae, H., Kimura, E., Ochiai, K. (2013). Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): A randomised, controlled, open-label trial. Lancet Oncology, 14(10), 1020–1026. https://doi.org/10.1016/S1470-2045(13)70363-2

Katsumata, N., Yasuda, M., Takahashi, F., Isonishi, S., Jobo, T., Aoki, D., Noda, K. (2009). Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3, open-label, randomised controlled trial. Lancet, 374(9698), 1331-1338. https://doi.org/10.1016/S0140-6736(09)6157-0

Maccaroni, E., Bracci, R., Lampieri, R., Bianchi, F., Belvedere, L., Brugiati, C., Berardi, R. (2016). Hypersensitivity reactions to antineoplastic agents in BRCA-mutated ovarian cancer patients: A single centre experience. Annals of Oncology, 27(suppl 6), iv77–iv79. https://doi.org/10.1093/annonc/mdw374

Makrillos, N., Syrigou, E., Kaklamanos, I., Manolopoulos, L., & Saif, M. W. (2010). Hypersensitivity reactions associated with platinum antineoplastic agents: A systematic review. Metal-Based Drugs, 2010, Article ID 207084. https://doi.org/10.1155/2010/207084

Markman, M., Kennedy, A., Webster, K., Elson, P., Peterson, G., & Belinson, B. (1999). Clinical features of hypersensitivity reactions to carboplatin. Journal of Clinical Oncology, 17(4), 1141–1145. https://doi.org/10.1200/JCO.1999.17.4.114

Matulonis, U. A., Sood, A. K., Fallowfield, L., Howitt, B. E., Sehouri, J., & Karlan, B. Y. (2016). Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. Nature Reviews Disease Primers, 2, 16062. https://doi.org/10.1038/nrdp.2016.62

Miki, Y., Swensen, J., Shattuck-Eidens, D., Futreal, P. A., Harshman, K., Tavtigian, S.,……Ding, W. (1994). Strong association of breast cancer with BRCA1. Science, 266(5182), 1331–1338. https://doi.org/10.1126/science.7545954

Moon, D. H., Lee, J.-M., Noonan, A. M., Annunziata, C. M., Mansell, L., Houston, N.,……Kohn, E. C. (2013). Deleterious BRCA1/2 mutation is an independent risk factor for car-

AdvancedPractitioner.com Vol 10 • No 5 • July 2019
boplatin hypersensitivity reactions. British Journal of Cancer, 109, 1072–1078. https://doi.org/10.1038/bjc.2013.389

Navo, M., Kunthur, A., Badell, M. L., Coffer, L. W., II, Markman, M., Brown, J., & Smith, J. A. (2006). Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. Gynecologic Oncology, 103(2), 608–613. https://doi.org/10.1016/j.ygyno.2006.04.002

O’Cearbhaill, R., Zhou, Q., Iasonos, A., Hensley, M. L., Tew, M. P., Aghajanian, C.,...Sabbatani, P. J. (2010). The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin re-treatment. Gynecologic Oncology, 116(3), 326–331. https://doi.org/10.1016/j.ygyno.2009.10.070

Ozols, R. F., Bundy, B. N., Greer, B. E., Fowler, J. M., Clarke-Pearson, D., Burger, R. A.,...Baergen, R. (2003). Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. Journal of Clinical Oncology, 21(17), 3194–3200. https://doi.org/10.1200/JCO.2003.02.153

Picard, M., & Castells, M. C. (2015). Re-visiting hypersensitivity reactions to taxanes: A comprehensive review. Clinical Reviews in Allergy & Immunology, 49(2), 177–191. https://doi.org/10.1007/s12098-014-8416-0

Pignata, S., Scambia, G., Katsaros, D., Gallo, C., Pujade-Lauraine, E., De Placido, S.,...Perrone, F. (2014). Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): A randomised, multicentre, open-label, phase 3 trial. Lancet Oncology, 15(4), 396–405. https://doi.org/10.1016/S1470-2045(14)70049-X

Schwartz, J. R., Bandera, C., Bradley, A., Brard, L., Legare, R., Granai, C. O., & Dizon, D. S. (2007). Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants’ Hospital. Gynecologic Oncology, 105(1), 81–83. https://doi.org/10.1016/j.ygyno.2006.10.047

U.S. Food & Drug Administration. (2016). FDA grants accelerated approval to new treatment for advanced ovarian cancer. Retrieved from https://www.fda.gov/Newsroom/PressAnnouncements/ucm533873.htm

Vasey, P. A., Jayson, G. C., Gordon, A., Gabra, H., Coleman, R., Atkinson, R.,...Kaye, S. B. (2004). Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. Journal of the National Cancer Institute, 96(22), 1682–1691. https://doi.org/10.1093/jnci/djh323

Zanotti, K. M., & Markman, M. (2001). Prevention and management of hypersensitivity reactions. Drug Safety, 24(10), 767–779. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11676304
### Appendix A. Allergies to Specific Agents Between Groups

| Agent              | BRCA wild-type (n = 49) | BRCA mutated (n = 13; BRCA1 = 9; BRCA2 = 4) |
|--------------------|-------------------------|---------------------------------------------|
| Medications        |                         |                                             |
| Penicillin         | 14                      | Penicillin                                  |
| Sulfa              | 1                       | Sulfa                                       |
| Amoxicillin        | 2                       | Bactrim                                     |
| Erythromycin       | 2                       | Avelox                                      |
| Levofoxacin        | 3                       | Cipro                                       |
| Cephalexin         | 2                       | Nitrofurantoin                              |
| Biaxin             | 1                       | Pyridium                                    |
| Flagyl             | 1                       | Demerol                                     |
| Gemzar             | 2                       | Codeine                                     |
| Albumin-colloid    | 1                       | Darvocet                                    |
| Codeine            | 3                       | Propoxyphene                                |
| Percocet           | 2                       | Captopril                                   |
| Reclast            | 1                       | Carboplatin                                 |
| Morphine           | 3                       | Cardizem                                    |
| Xanax              | 1                       | Lovastatin                                  |
| Phenothiazines     | 1                       | Simvastatin                                 |
| Compazine          | 3                       | Magnesium                                   |
| Phenergan          | 1                       | Benzonatate                                 |
| Loratt             | 1                       | Miscellaneous                               |
| Benadryl           | 1                       | Adhesive                                    |
| Steroids           | 1                       | Pineapple                                   |
| Dextromethorphan   | 1                       | Egg                                         |
| Tegaderm           | 2                       | Avocado                                     |
| TYLENOL            | 1                       | Dairy products                              |
| Iodine             | 1                       | Peanuts                                     |
| Miscellaneous      |                         | Dust                                        |
| Cigarette smoke    | 1                       |                                             |
| Diesel fumes       | 1                       |                                             |
| Shellfish          | 1                       |                                             |
| Nickel             | 1                       |                                             |
| Adhesive           | 7                       |                                             |
| Latex              | 3                       |                                             |
| Pollen             | 1                       |                                             |
| Citrus nuts        | 1                       |                                             |
| Corn               | 1                       |                                             |
| Metals             | 1                       |                                             |
| Lactose            | 1                       |                                             |
| Artificial sweeteners | 1                    |                                             |
| Green tea          | 1                       |                                             |
| Thyme              | 1                       |                                             |
| Mushrooms          | 1                       |                                             |
| Wool               | 1                       |                                             |