Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2012;74:21–27
DOI: 10.1159/000336772

Received: April 6, 2011
Accepted after revision: January 24, 2012
Published online: May 31, 2012

# A Search for Predictive Factors for Hypersensitivity Reactions to Paclitaxel and Platinum Salts in Chemotherapy for Gynecologic Pelvic Neoplasms

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**Key Words**
Chemotherapy · Gynecologic pelvic neoplasms · Hypersensitivity reactions · Paclitaxel · Platinum salts

**Abstract**
***Aims:*** To investigate the frequency of and predictive factors for hypersensitivity reactions (HR) to taxanes and platinum salts in a cohort of patients treated for pelvic gynecologic malignancies. ***Methods:*** The medical records of all patients with gynecologic pelvic neoplasms treated with chemotherapy at the Department of Gynecologic Oncology, AO Mauriziano Umberto I of Turin, from September 2007 through August 2008, were retrospectively reviewed. Two multivariate models, regarding carboplatin and taxane chemotherapy, respectively, were performed to evaluate the potential predictive value of various clinical features. ***Results:*** The incidence of HR was 14% (22/157). Multivariate models showed that menopausal women had a significantly lower probability of HR (OR 0.12, CI 0.02–1.13, p = 0.06 for the carboplatin model and OR 0.05, CI 0.01–0.63, p = 0.02 for the taxane model) while a history of systemic hypersensitivity was associated with a higher but non-significant risk of HR (OR 2.64, CI 0.78–8.95, p = 0.11, for the carboplatin model and OR 3.42, CI 0.94–12.45, p = 0.06, for the taxane model). ***Conclusion:*** We confirmed a history of hypersensitivity as a risk factor for HR. Other larger cohorts should be analyzed: we need to find new predictive factors in order to select women who should be submitted to experimental prophylactic strategies.

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## Introduction

Paclitaxel and platinum salts (carboplatin, cisplatin, oxaliplatin) are highly active antineoplastic agents used to treat gynecologic pelvic neoplasms (endometrial, cervical and ovarian cancer) and in other malignancies [1]. Hypersensitivity reactions (HR) to paclitaxel and platinum salts still represent a major concern, despite the fact that several strategies to avoid them have been tested [2, 3].

Mild-to-moderate HR (grades 1 and 2 according to the National Institutes of Health Common Terminology Criteria for Adverse Events) are identified as flushing, rash or fever which regress spontaneously or respond promptly to symptomatic treatment. Severe HR (grades 3 and 4) are associated with prolonged symptoms, which do not respond rapidly to treatment, with possible clinical sequelae (pulmonary infiltrates, renal impairment).

Anaphylaxis (grades 3 and 4) is characterized by symptomatic bronchospasm with dyspnea and dizziness,

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0378–7346/12/0741–0021$38.00/0

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| Adverse event | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Allergic reaction | Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated | Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 h | Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. | | | | | |
| Anaphylaxis | – | – | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/ angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. | | | | | |

**Fig. 1.** Allergic reaction and anaphylaxis according to CTCAE Version 4.0 published May 28, 2009 (v4.03: June 14, 2010) by the US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

urticarial, edema or angioedema, hypotension and loss of consciousness (fig. 1).

When a patient develops an HR to an antineoplastic agent, the drug often has to be discontinued, thus raising a dilemma for the healthcare professional: further use may cause a severe allergic reaction on re-exposure, but alternative drugs may be less effective or poorly tolerated.

The objective of this study was to investigate the frequency of and predictive factors for HR to paclitaxel and platinum salts in a cohort of patients treated for pelvic gynecologic malignancies.

## Materials and Methods

We retrospectively reviewed the records of all patients with pelvic gynecologic malignancies treated with chemotherapy in the Department of Gynecologic Oncology at the Mauriziano Umberto I Hospital in Turin, from September 2007 through August 2008. We recorded data regarding the type of malignancy and chemotherapy, the number of courses administered, HRs, age, body mass index (BMI), menopausal status, history of systemic hypersensitivity, cardiovascular diseases, use of premedication, previous chemotherapy and the number of previous courses with platinum salts.

An unconditional univariate logistic model was applied to evaluate the potential of a number of clinical features as predictive factors for HR: BMI (>25 or <25), site of primary neoplasm, menopausal status at treatment start time (yes/no), history of cardiovascular disease (yes/no), history of systemic hypersensitivity (yes/no) and oral premedication (yes/no), with age as a continuous variable.

A multivariate logistic regression analysis was then fitted, including BMI, menopausal status, history of systemic hypersensitivity (dichotomous variables), age and total number of previous carboplatin chemotherapy courses administered (continuous variables), restricting our analysis to the patients in our cohort who received this drug. A second model was fitted that included oral premedication rather than previous carboplatin chemotherapy courses, and this was applied only to those patients receiving paclitaxel.

A variable was considered prognostically significant when the p value was $<0.05$. Statistical analyses were carried out using Stata 9.1, release 9.1 (Stata Corp., College Station, Tex., USA).

## Results

From September 2007 through August 2008, 157 patients were treated with chemotherapy in our department. 109 were suffering from ovarian cancer, 23 by endometrial cancer, 21 by cervical cancer, and 4 by another primary gynecological malignancy. Six patients had a double neoplasm. A history of systemic hypersensitivity was referred by 40.9% of HR cases and by 19.3% of patients who did not develop HR (table 1). Details on all the



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**Table 1.** Patients' characteristics

| | HR group (n = 22) | Non-HR group (n = 135) |
|---|---|---|
| Prior history of systemic hypersensitivity | 40.9% (9/22) | 19.3% (26/135) |
| Site of primary tumor | | |
| Ovary | 72.7% (16/22) | 68.9% (93/135) |
| Endometrium | 13.6% (3/22) | 14.8% (20/135) |
| Cervical | 13.6% (3/22) | 13.3% (18/135)[a] |
| Postmenopausal status at the time of CT | 72.7% (16/22) | 97% (131/135) |
| BMI ≤25 | 63.6% (14/22) | 48.2% (65/135) |
| Mean age ± SD | 52.5 ± 11 | 59 ± 12.3 |
| Cardiovascular disease | 31.8% (7/22) | 43.7% (59/135) |

[a] Four patients had a primary gynecologic neoplasia, different from cervical, ovarian and endometrial cancer.

**Table 2.** Chemotherapy regimens

| Regimen | Patients |
|---|---|
| Carboplatin-paclitaxel | 65 |
| Paclitaxel | 6 |
| Carboplatin | 11 |
| TIP (paclitaxel, ifosfamide, cisplatin) | 20 |
| TEP (paclitaxel, epirubicin, cisplatin) | 5 |
| Other (not containing paclitaxel or platinum salts) | 50 |

chemotherapy regimens administered are shown in table 2. We used only brand-name drugs.

All the patients received antiemetic premedication: granisetron or tropisetron and dexamethasone (12 mg). The patients treated with a combination of a platinum salt and paclitaxel were administered 125 mg oral aprepitant 1 h before starting chemotherapy infusion and 0.25 mg intramuscular palonosetron 30 min prior to infusion. All patients treated with paclitaxel received a short course of in-hospital premedication with an $H_1$ antagonist (chlorpheniramine 10 mg) and an $H_2$ antagonist (ranitidine 100 mg) in addition to dexamethasone given as an antiemetic. All patients treated with paclitaxel were offered oral premedication with 25 mg prednisone, 1 mg dimethindene maleate and 300 mg ranitidine to be taken at home the evening before the chemotherapy, but only 39.3% of them (37/94) took it.

The average age was 58.13 years (standard deviation (SD) 12.3), 52.5 (SD 11) in the HR group and 59 (SD 12.3) for non-HR patients; BMI was <25 in 63.6% and 48.2% in the HR and non-HR groups, respectively. The overall incidence of HR was 14% (22/157). Among cases of HR, 11/22 reacted to carboplatin, 10/22 reacted to paclitaxel, and 1/22 reacted to liposomal doxorubicin.

The incidence of HR to paclitaxel was 10% (10/96). The incidence of HR to carboplatin was 14% (11/76). We observed no HR to cisplatin (0/25).

In 90 patients, platinum agents and paclitaxel were coadministered and among those patients we observed 20 HR (22%). 20 patients were treated with TIP (paclitaxel, ifosfamide, cisplatin) and 3 of them reacted to paclitaxel. 5 patients were treated with TEP (paclitaxel, epirubicin, cisplatin) and 2 of them reacted to paclitaxel. 65 patients were given carboplatin and paclitaxel: 5 of them reacted to paclitaxel and 10 reacted to carboplatin.

HR occurred during frontline chemotherapy in 10 patients and during therapy for recurrent disease in 12 patients. Patients who reacted to paclitaxel had a median cumulative number of null prior courses of paclitaxel; only 1 patient had one previously infused course of paclitaxel and 9 patients were on their first course of chemotherapy. Patients who reacted to carboplatin had a median cumulative number of 8.5 prior courses of carboplatin. HR varied depending on the causative agent, but most commonly included flushing, dyspnea/bronchospasm, back pain, chest discomfort, pruritus, erythema, nausea and alterations in blood pressure or pulse rate. 19 out of 22 patients developed moderate or severe HR. All cases were handled with the immediate termination of the infusion, followed by intravenous steroids, antihistamines, and fluids. Symptoms resolved completely within several hours in all patients.

A preliminary analysis of patients who developed HR showed that 50% of these patients had previously been treated with carboplatin, 60% had taken premedication at home the day before chemotherapy infusion and 62% were menopausal at treatment start time. 60% of patients who developed HR had a history of systemic hypersensitivity to drugs, environmental or animal exposure and 31% had a history of cardiovascular disease. In the univariate logistic model, BMI, age, site of primary neoplasm and cardiovascular disease history did not prove indicative of a significantly increased risk of HR. The first multivariable model, analyzing only patients treated with carboplatin and including the number of carboplatin chemotherapy courses, showed a lower risk of HR for menopausal status at treatment start time (OR 0.12, CI



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**Table 3.** Risk factors for HR

| | Platinum salts (n = 101) | | | Paclitaxel (n = 96) | | |
|---|---|---|---|---|---|---|
| | OR[a] | 95% CI | p value | OR[a] | 95% CI | p value |
| Postmenopausal status at the time of CT | 0.12 | 0.02–1.13 | 0.06 | 0.05 | 0.01–0.63 | 0.02 |
| Prior history of systemic hypersensitivity | 2.64 | 0.78–8.95 | 0.11 | 3.42 | 0.94–12.45 | 0.06 |
| BMI >25 | 0.61 | 0.20–1.93 | 0.40 | 0.68 | 0.21–2.21 | 0.52 |
| Age | 0.97 | 0.92–1.02 | 0.20 | 0.98 | 0.93–1.04 | 0.20 |
| Number of carboplatin courses | 1.08 | 0.97–1.20 | 0.16 | | | |
| Oral premedication | | | | 1.56 | 0.47–5.16 | 0.47 |

[a] Adjusted for all variables in the column.

0.02–1.13, p = 0.06); BMI >25 was associated with a lower but non-significant risk of HR (OR 0.61, CI 0.20–1.93, p = 0.40). Age was not associated with a higher risk of HR (OR 0.97, CI 0.92–1.02, p = 0.20). A history of systemic hypersensitivity was associated with a higher risk of HR (OR 2.64, CI 0.78–8.95, p = 0.11). The number of chemotherapy courses administered did not have an impact on HR risk (OR 1.08, CI 0.97–1.20, p = 0.16).

In the second model we restricted our analysis to patients on treatment regimens containing paclitaxel, including the oral premedication variable (OR 1.56, CI 0.47–5.16, p = 0.47). Here, once again, other independent variables did not show a significant variation, except in the case of a history of systemic hypersensitivity, which was associated with a higher risk of HR (OR 3.42, CI 0.94–12.45, p = 0.06) (table 3).

## Discussion

The international standard first-line treatment of advanced ovarian cancer is the combination of a taxane (usually paclitaxel but sometimes docetaxel) and a platinum agent [4] administered after cytoreductive surgery. These drugs are used, in different combinations and schedules, to treat platinum-sensitive ovarian cancer relapses, cervical and endometrial cancer in association with radiotherapy and also advanced or recurrent endometrial cancer [5–13]. These multidrug regimens are often limited by the occurrence of HR and the features of this type of toxicity are not yet clear.

The rate of HR associated with paclitaxel regimens is up to 30% without premedication therapy and 2–4% with premedication (steroids and antihistamines) [2, 14]. Although there are reports suggesting that a history of allergies increases the incidence of HR to paclitaxel, no IgE-mediated mechanism has been established. The exact mechanism responsible for HR to platinum salts is also unknown: HR to carboplatin (12–30%) seems to be more frequent than HR to cisplatin (5–20%) [3, 15, 16].

Our study has two main strong points: it is the first study to look for common risk factors for HR in ovarian, endometrial and cervical cancer chemotherapy, and it had a high level of follow-up (we only lost 1 patient, who did not develop HR). Moreover, while retrospective studies can be limited and incomplete, we used clinical records to find all data, thus minimizing the possibility of recall bias.

We used a parsimonious statistical approach: in order to minimize confounding we used only five independent variables in the logistic regression model, (postmenopausal status, history of hypersensitivity, obesity and age) as there were only 22 cases of HR. For the carboplatin and paclitaxel chemotherapy models, the variables used were the number of carboplatin courses and oral premedication, respectively.

Recent studies have begun to evaluate the role of pharmacogenomics in the toxicity of taxane plus platinum chemotherapy in ovarian cancer: the interindividual differences in HR are probably due to the action of multiple genes. Along with these genetic risk factors there are also environmental risk factors that are as yet only partially adjustable and not fully understood [17–19].

Sendo et al. [20] found five HR risk factors for hypersensitivity to paclitaxel: a history of dermal allergic reactions, respiratory dysfunction, obesity, postmenopausal and non-drinker status, in 14 cases of HR. Our study, on the other hand, included different chemotherapy regimens for gynecologic pelvic cancers, and while these studies are not completely comparable, our data did not



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confirm previous results. In our study, postmenopausal status appeared to have a protective OR for HR (a causal link between the oscillations of sex hormones and the overall allergic response has recently been suggested by De Oliveira et al. [21]), while Sendo et al. [20], with a similar number of cases, had the opposite results: this can be explained by the small number variability. In our cohort only 10 patients were not postmenopausal.

In all our models, a history of hypersensitivity represented a risk factor for HR: in the model restricted to carboplatin this risk was 2.64 (CI 0.78–8.95), while among patients treated with paclitaxel it was 3.42 (CI 0.94–12.45). A few other studies in the literature have attempted to test the predictive value of patients' clinical or anamnestic features in terms of HR to platinum salts or paclitaxel. Grosen et al. [22] published an interesting retrospective case-control study according to which a history of bee-sting allergy or animal allergy was associated with an increased risk of HR to paclitaxel. Markman et al. [23] analyzed patients with a history of systemic hypersensitivity to medication or environmental exposure (e.g. bee-stings) and concluded that these patients may have a heightened risk of allergic reactions to carboplatin.

The incidence of HR to carboplatin was 14% (overlapping with literature data), falling to 10% with paclitaxel. The latter result is above the upper limit of the range reported in the literature (2–4%) [2, 14], but we reported all HR, even if G1–2 and a low level of compliance with premedication regimens. In accordance with the international literature [24], the incidence of HR was higher in ovarian cancer.

We divided BMI into two categories, in line with the international literature. In our cohort, 78 patients had a BMI >25 and 79 had a BMI ≤25, respectively 8 and 14 among cases. This frequency may have affected the result of our study, compared to the study of Sendo et al. [20]: we found a protective effect for a BMI >25, compared to the 9-fold higher risk in the Japanese cohort. The difference can also be attributed to variability, in view of the small number of cases and the large difference in the number of cases among the two HR groups. It may also be related to the different body mass characteristics of Asian and European women.

Few studies have investigated the relationship between BMI and atopy. A recent study on an adult population suggests a significant association between obesity and atopy [25]. However, a series of studies in pediatric populations have reached the opposite conclusion [26–28].

We included previous carboplatin chemotherapy courses in our model restricted to carboplatin chemotherapy regimens: according to the literature, HR to paclitaxel are generally immediate, occurring during the first few minutes of the I and II infusions, while reactions to platinum salts occur after multiple therapy cycles and the median number of platinum (carboplatin or cisplatin) courses before the first reaction is generally 8–9 (8.5 in our study) [3, 14, 29–35]. However, in our model restricted to carboplatin chemotherapy, the additional risk for patients previously treated with carboplatin was minimal (OR = 1.08), and not statistically significant. According to the literature [16, 35] these patients can undergo a skin test to identify those at risk for HR to carboplatin before HR occurs. According to Zanotti et al. [35], patients who have received more than six courses of platinum-based treatment should have an intradermal skin test using the carboplatin preparation that is to be infused. Leguy-Seguin et al. [3] used skin tests to predict potential cross-reactions in patients selected to continue treatment with a different platinum salt following a platinum HR. In three studies [36–38], deaths were reported due to anaphylaxis following cisplatin. Kandel et al. [39] concluded that cisplatin rechallenge is a feasible strategy to overcome carboplatin hypersensitivity.

We performed a second model limited to patients treated with paclitaxel: phase 1 trials on taxanes conducted in the late 1980s were almost halted because of the high frequency of HR with respiratory distress, hypotension, angioedema, flushing, urticaria, and chest, abdomen, and extremity pain occurring on the first or second exposure in the majority of cases [14]. In our multivariable analysis we also included the oral premedication variable. Premedication therapy probably does not eliminate reactions, but it does minimize the incidence and severity of symptoms.

The prophylactic regimen (advance premedication) with dexamethasone at a dose of 20 mg given orally 12 and 6 h before paclitaxel infusion, and intravenous $H_2$ antagonist and oral diphenhydramine 30 min before infusion proved to reduce the incidence of paclitaxel-induced HR significantly [40] but requires good patient compliance. This compliance is not always easy to achieve: in our study only 37 out of 94 patients who were prescribed the oral home premedication took it correctly. Patients are often psychologically frail during chemotherapy and many of them think that taking other drugs in addition to chemotherapy might further damage their bodies: they therefore take prescribed premedication only intermittently. This underlines the importance of the physician providing a detailed explanation of the purpose, the safety and the importance of premedication.



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Our result, i.e. a higher risk for patients receiving oral premedication, is not statistically significant and is likely to be affected by the small number of patients in this model (95/157); oral premedication is probably a proxy variable of patients' compliance to therapy. History of hypersensitivity suggests a higher risk of HR for patients receiving paclitaxel than carboplatin chemotherapy regimens. This result needs to be confirmed with a larger cohort but according to this data, patients treated with paclitaxel, on their first or second course, and especially those with a history of hypersensitivity, should be closely followed by a nurse during infusion. These patients could be candidates for a test dose of paclitaxel prior to being administered the full dose [41].

Some limitations must be considered while interpreting our results: we performed a retrospective analysis because of the type of cohort. Moreover, our results sometimes diverge from the international literature: this is logical due to the small number of HR cases in existing studies on this topic. Large variability could also produce divergent results. Our study suggests that a history of systemic hypersensitivity is a risk factor for HR to paclitaxel and platinum, but further, larger studies are needed to define new predictive factors for HR: we cannot rule out an element of chance in our results, but they do suggest a trend of high risk for patients with a history of systemic hypersensibility. Establishing predictive clinical features represents one way of optimizing the management of patients treated with chemotherapy, identifying candidates for experimental programs of skin/dose tests, intense premedication or desensitization, or those who simply require to be closely followed by nurses. In addition to careful monitoring, patients with risk factors should be strongly encouraged to take the prescribed premedication at home and to inform healthcare professionals of any discomfort during the infusion as soon as possible.

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