Administration of cisplatin in three patients with carboplatin hypersensitivity: is skin testing useful?

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Carboplatin is a chemotherapeutic agent approved in the first-line setting of numerous malignancies. Hypersensitivity to carboplatin has been reported in up to 44% of patients receiving this antineoplastic agent, usually occurring after several courses of treatment. The aim of this study was to determine the usefulness of skin tests in ruling out cross-reaction to cisplatin to continue platinum-based chemotherapy in patients who are responsive to these agents. Prick tests and intradermal tests with a series of dilutions of carboplatin and cisplatin were performed on three patients who had exhibited medium and severe hypersensitivity reactions to carboplatin. Prick tests were negative in both the antineoplastic agents. Intradermal tests with carboplatin were positive in all three patients and negative with cisplatin. In all patients, the administration of cisplatin instead of carboplatin was well tolerated without the need of premedication. In conclusion, intradermal skin tests can be a useful tool for detecting a potential cross-reaction between platinum salts. It allows safe administration of a different platinum agent in patients who seem to benefit from platinum-based therapy. Discontinuation of chemotherapy, desensitization protocols and steroid premedication can be avoided. ***Anti-Cancer Drugs*** **21:333–338 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Hypersensitivity to a chemotherapeutic agent is defined as an unforeseen reaction whose signs and symptoms cannot be explained by the known toxicity profile of the drug [1]. Hypersensitivity reactions to industrially complex platinum salts were first described in 1945 among refinery workers [2]. In the 1970s, there were the first reports of platinum hypersensitivity reactions upon the use of cisplatin in patients who had received the drug earlier [3]. Carboplatin [*cis*-diamine-1,1-cyclobutane dicarboxylate platinum (II)] differs from cisplatin in that a 1,1-cyclobutane dicarboxylate group substitutes the two chlorides in cisplatin. It exhibits a favorable toxicity profile and can reduce the dose-limiting cisplatin side effects, including nephrotoxicity and neurotoxicity [4–6]. Platinum-based agents are a standard component of the initial chemotherapy regimens for ovarian cancer and primary peritoneal carcinoma and are also used to treat bladder, lung, esophageal, testicular, or endometrial cancer [6–8]. Carboplatin has also proven to be effective for pediatric tumors including ependymomas, low-grade gliomas, and primitive neuroectodermal tumors [9]. It is an increasingly preferred agent for the palliative treatment of recurrent disease, particularly in patients with a long retreatment-free interval after initial treatment with this cytotoxic drug [10].

The overall incidence of hypersensitivity reactions to carboplatin can reach 44% according to some studies [11–13]. Carboplatin hypersensitivity is more frequently observed after several courses of treatment and is mainly attributed to types I and IV allergic reactions. Symptoms can range from mild to severe and may even lead to death [12].

There is no common strategy followed after hypersensitivity reaction to chemotherapy. In patients who seem to benefit from platinum-based therapy, it would be valuable to be able to continue treatment with a different platinum agent. Skin testing can help rule out cross-reaction to other platinum agents, allowing the administration of cisplatin instead of carboplatin and avoiding the need for discontinuation, premedication, or desensitization.

Methods

Patients

We report three cases of patients who exhibited carboplatin-associated hypersensitivity. All had received carboplatin in their initial doublet therapeutic regimen. The first patient was a 62-year-old male who was diagnosed with mesothelioma in December 2006. He had an unremarkable medical history and no history of allergies. He had occupational exposure to asbestos and

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presented with persistent cough for the previous 2 months. The chest radiograph revealed a right lung shadowing and the computed tomography (CT) scan showed abnormal thickening of the right pleura. The open lung biopsy showed mesothelioma of the epithelial type. CT scans of the abdomen and brain and bone scanning revealed no metastases. The patient received six cycles of first-line chemotherapy with tri-weekly carboplatin area under the curve (AUC) 5 and pemetrexed (500/m^2) from December 2006 to March 2007. New CT scans showed that there was partial response to the disease and the patient was subsequently under regular follow-up examination. In June 2008, the chest CT scan revealed progression of the lung disease and the patient started receiving second-line treatment with the same therapeutic regimen because of the good response he exhibited in the first-line setting. During the second cycle of the second-line regimen, the patient experienced flushing (grade I hypersensitivity reaction) near the end of the infusion, which subsided when the infusion was discontinued. During the third infusion, 10 min after initiation of treatment, the patient exhibited a grade III hypersensitivity reaction with symptoms of hypotension (systolic pressure/diastolic pressure: 70/40), tachypnoea, diaphoresis, bronchospasm, facial flushing, erythema of the trunk and extremities. The symptoms gradually subsided with infusion termination and administration of adrenaline intramuscularly, oxygen, salbutamol inhalation and intravenous (i.v.) normal saline, antihistamines and corticosteroids. It should be noted that the patient exhibited a hypersensitivity reaction even though he was already receiving the standard steroid premedication for pemetrexed (4 mg dexamethazone twice daily the day before, on the day of and the day after the infusion). The new CT scans showed partial response of the tumor but owing to the carboplatin-related hypersensitivity, the regimen was altered to biweekly docetaxel (80 mg/m^2) and gemcitabine (1 g/m^2). CT scans after three full cycles of this regimen revealed disease progression in the lungs, as well as liver and adrenal gland metastases. Owing to the patient's nonresponse to the new regimen and his previous response to carboplatin, we performed skin testing to rule out cross-sensitivity to cisplatin to use cisplatin instead of carboplatin in the third-line setting.

The second patient was a 69-year-old male who was diagnosed with non-small-cell lung cancer (of the adenocarcinoma histological subtype) in August 2008. Before diagnosis, no allergies were observed. The only concomitant disease was hypertension, which was treated with candesartan. The patient had experienced weight loss and hemoptysis and the chest CT scan revealed a tumor in the upper right lung lobe as well as multiple tumor nodules in the contralateral lung. CT scan of the abdomen revealed a single metastatic lesion in the liver and one in the left adrenal gland. The histological examination of the open lung biopsy tissue showed lung adenocarcinoma of medium and low differentiation. The patient started receiving first-line chemotherapy with biweekly docetaxel (70 mg/m^2) and carboplatin (AUC4). During the seventh infusion of carboplatin (fourth cycle of first line), the patient exhibited a grade II hypersensitivity reaction during the first few minutes of carboplatin infusion (dyspnea, rash, flushing and abdominal cramping). It should be noted that the patient was already receiving the standard steroid premedication for docetaxel (8 mg dexamethazone twice daily for 3 days starting 1 day before infusion). The symptoms of the allergic reaction subsided with the administration of oxygen, inhalation of salbutamol and intravenous (i.v.) normal saline, antihistamines, and corticosteroids. New CT scans showed partial response of the disease (the liver and adrenal gland metastases had disappeared and all lung nodules had smaller dimensions). We decided to perform skin testing to determine whether carboplatin could be substituted with cisplatin to continue platinum-based therapy in this platinum-sensitive patient.

The third patient was 65-year-old female who was diagnosed with ovarian cancer in February 2008. She had no history of allergies and the only concomitant diseases were hypertension (treated with combination of amlodipine and valsartan) and diabetes mellitus (treated with metformin hydrochloride). The patient had been experiencing progressive abdominal discomfort and swelling. A CT scan revealed ascites, swollen retroperitoneal lymph nodes, and omentum lesions. Paracentesis was performed and the cytological examination of the ascitic fluid sample revealed adenocarcinoma cells consistent with ovarian cancer. The patient was then submitted to total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic and para-aortic lymphadenectomy. Histological examination of the tissue removed confirmed the initial diagnosis of ovarian cancer extending to both ovaries, fallopian tubes, the uterus, the omentum and retroperitonal lymph nodes. The patient received four cycles of adjuvant chemotherapy with triweekly carboplatin AUC 6 and paclitaxel (200/m^2) from March to June 2008. CT scans revealed no tumors and the patient was under regular follow-up examination. In November 2008, there was disease progression with new pelvic masses and a lung lesion in the right lower lobe. Biopsy revealed that this tumor was secondary to the initial ovarian carcinoma. The patient started receiving first-line chemotherapy with biweekly i.v. gemcitabine (1000/m^2) and docetaxel (80/m^2) but there was an increase in the ascites and new CT scans revealed disease progression in the abdominal masses. The patient was then submitted to triweekly i.v. carboplatin AUC 6 and topotecan (3/m^2) infusions. During the third carboplatin infusion (third cycle of the second line), the patient exhibited a grade II hypersensitivity reaction with dyspnea, nausea, and urticaria. These symptoms subsided with oxygen, inhalation of salbutamol and i.v.

normal saline, antihistamines, and corticosteroids administration. New CT scans showed partial response of the disease (smaller dimensions of the lung tumor and pelvic masses). We decided to perform skin testing to rule out cross-sensitivity to cisplatin to continue with platinum-based chemotherapy in the second-line setting.

Experiments

To rule out the possibility of platinum cross-reactivity, we performed skin testing in all three patients. The tests were performed after a minimal period of 2 weeks following the adverse reaction and consisted of skin-prick testing and intradermal tests (IDs).

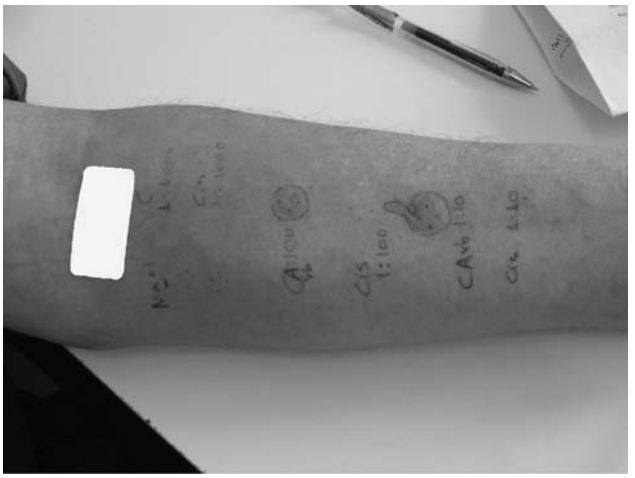
First, prick tests were performed on the forearm of each patient with a pure injectable form of carboplatin and cisplatin, using 0.9% saline and 10 mg/ml histamine as negative and positive controls, respectively. A positive test was defined when a wheal 3 mm larger in diameter than the negative control with surrounding erythema was present 20 min later. IDs were performed on the volar surface forearm by using a sterile solution of carboplatin and cisplatin, diluted sequentially (10^{-3}, 10^{-2}, 10^{-1}) in 0.9% saline. The dilutions were performed an hour before the procedure. The injection of 0.02–0.04 ml produced a 4–6 mm weal. Negative control was performed using 0.9% saline sodium. For an ID to be considered positive, the initial weal was expected to be at least 3 mm larger in diameter than the negative control at the 20-min reading and to have a surrounding flare. The ID was examined again at 24 and 48 h [14].

Results

In all three patients, all prick tests were negative at the 20-min reading. In the first and second patient, the ID was positive at a dilution of 10^{-2} of carboplatin at the 20-min reading and negative 24 and 48 h later (Figs 1 and 2). The third patient had a positive ID at a dilution of 10^{-3} of carboplatin on immediate reading at 20 min (Fig. 3). The ID was negative with all dilutions of cisplatin at the 20 min, 24 and 48 h readings in all patients; therefore, it was decided to go ahead with cisplatin administration.

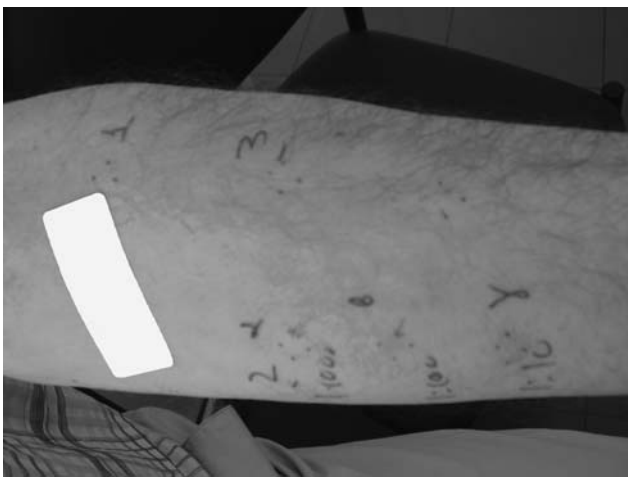
The first patient started third-line therapy with triweekly i.v. cisplatin (80/m^2) and pemetrexed (500/m^2). No allergic reaction has been observed after three infusions and the new CTs showed partial response with smaller lesion dimensions. The second patient continued first-line chemotherapy with triweekly cisplatin (80/m^2) and docetaxel (80/m^2) and is showing improvement in his

Fig. 2



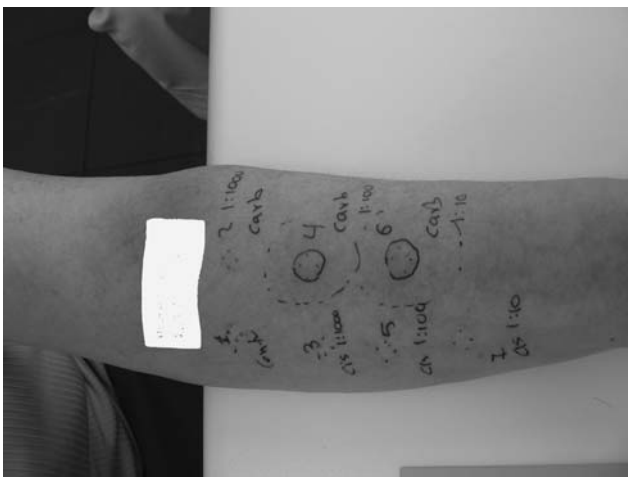
Results of the intradermal test in the second patient at the 20-min reading.

Fig. 1



Results of the intradermal test in the first patient at the 20-min reading.

Fig. 3



Results of the intradermal test in the third patient at the 20-min reading.

clinical status after two infusions. No adverse drug reaction has been observed in this patient either. The third patient continued second-line chemotherapy with triweekly i.v. cisplatin (80/m^2) and topotecan (3/m^2), and after two infusions no hypersensitivity reaction has been noticed. Restaging CTs showed partial response with the disappearance of the metastatic lung and abdominal lesions.

Discussion

Incidence of carboplatin-related hypersensitivity

A rise in the incidence of hypersensitivity reactions to all platinum salts is expected as a result of increasing clinical use. In contrast to the immediate hypersensitivity reactions to taxanes, the most striking feature of hypersensitivity after receiving carboplatin seems to be the development of the initial reaction after a significant number of carboplatin infusions in patients who had exhibited no allergic reaction until then [12,15].

In fact, the incidence of hypersensitivity seems to be correlated with the number of carboplatin cycles administered. In patients who have received fewer than six cycles of carboplatin, there is a 1% incidence of hypersensitivity reactions [16]. Markman *et al.* [12] reported this rate increasing to 27% in patients receiving more than seven cycles of carboplatin. The median number of infusions for the first allergic reaction to be manifested is eight [12,15,17,18] and half of these reactions are moderate to severe [12]. The incidence in the third-line retreatment has been reported to be as high as 44% [11,12]. Polyzos *et al.* [19] reported a 16% incidence of carboplatin hypersensitivity when the drug was administered intravenously but no allergic reaction was observed in the group receiving it intraperitoneally. Hypersensitivity reactions to cisplatinum are reported to have an incidence of 5–20%, which increases with radiation. Oxaliplatin is reported to cause hypersensitivity reactions in 12% of patients, but less than 1% of these are grade III and IV [20].

The fact that most hypersensitivity reactions occur during course 8 of carboplatin therapy has been attributed to the fact that patients are exposed to very low concentrations of 'free' platinum during each treatment [21,22]. Each carboplatin infusion seems to lower the threshold for the development of hypersensitivity reaction [23]. The patient is probably sensitized during the initial six-course regimen and further immunological stimulation during the reintroduction of the drug (course 7) is needed for an allergic reaction to manifest itself during course 8 [12].

Risk factors

There are several risk factors that are thought to take part in carboplatin hypersensitivity. HLA phenotype is a significant factor in the occupational sensitization to complex platinum salts and the intensity of exposure influences this impact [24]. A history of allergic reactions to medications and environmental exposures is associated with a modest but statistically significant risk of carboplatin hypersensitivity [21]. Multiple intermittent dosing schedules and rate of drug administration also seem to be key components [9].

Mechanisms: pathophysiology

Several studies have tried to explain the pathophysiology of carboplatin hypersensitivity but the exact mechanism is still debated. These reactions have mostly been described as type I IgE-mediated reactions or type IV T-cell-mediated hypersensitivity. In type I hypersensitivity reactions, IgE immunoglobulin binds with high affinity to mast cells and basophils and leads to their degranulation and to the nonimmune-mediated release of histamine and cytokines with vasoactive effect [1,4,12,16,25]. These substances are responsible for early-onset symptoms, such as itching, chest pain, and rash, as well as for anaphylactic reactions [12]. This mechanism is supported by hypersensitivity reactions observed in refinery workers exposed to platinum salts [2,17,22] by the prolonged period required for sensitization and the positive skin tests to carboplatin [2,26]. The haptopenic qualities of carboplatin have yet to be proven [5]. In the meantime, there seems to be an implication of type IV hypersensitivity, in which T-cells sensitized earlier are activated by antigens bound to the major histocompatibility complex. A delayed inflammatory reaction is initiated presenting with erythema and induration [27]. These type IV hypersensitivity reactions occur after repeated exposure and are observed within hours or even days after drug administration [12]. Types I and IV hypersensitivity reactions are distinguished mainly according to the onset of symptoms after i.v. administration of the drug [28]. Finally, platinum compounds have also been implicated in type II hypersensitivity reactions with hemolysis and thrombocytopenia [29]. There is an unpredictable presentation pattern of carboplatin-related hypersensitivity reactions, suggesting the involvement of multiple immunological and nonimmunological mechanisms [2,22].

Symptoms

Carboplatin hypersensitivity can either be acute, occurring during the infusion or several minutes after, or delayed, occurring hours or days after the infusion [12]. Hypersensitivity may first appear as a mild rash or itching days after the infusion. Fifty percent of these patients continue to develop reactions that range from mild to more severe that can even result in death. Mild reactions include edema on infusion arm, facial flushing, erythematous rash and palmar erythema, abdominal cramping and diarrhea, back pain, pruritus, dyspnea, and great anxiety. Severe reactions are bronchospasm, tachycardia, seizures, hypotension or hypertension, angina and hives, and a pattern consistent with anaphylaxis [1,2,4,12,17,

Table 1 Grades of hypersensitivity reactions according to the National Cancer Institute common terminology criteria for adverse events (version 3.0)

Grade	Description of hypersensitivity
I	Transient flushing or rash
	Drug fever <38°C (<100.4°F)
II	Rash
	Flushing
	Urticaria
	Dyspnea
	Drug fever ≥ 38°C (≥ 100.4°F)
III	Symptomatic bronchospasm, with or without urticaria
	Parenteral medication(s) indicated
	Allergy-related edema/angioedema
	Hypotension
IV	Anaphylaxis
V	Death

30–33]. Hypersensitivity reactions to carboplatin infusions are defined according to the Common Terminology Criteria of the National Cancer Institute (version 3.0) (Table 1) [34].

Treatment strategies

When a carboplatin-related hypersensitivity reaction occurs, drug infusion should immediately be ceased and replaced by saline infusion, an i.v. antihistamine drug and a low-dose corticosteroid administration. The dilemma facing clinicians is whether the platinum agent should be completely discontinued, especially in cases in which the patient has benefited from this drug.

Mild hypersensitivity has sometimes been treated with decrease in the infusion rate and with the use of corticosteroids and antagonists of histamine type 1 and 2 receptors as premedication before each administration, but this approach does not eliminate the risk of severe hypersensitivity reactions, despite its effectiveness in taxane hypersensitivity [35].

Several desensitization protocols of dose escalation schema have been used to readminister carboplatin after the occurrence of a severe hypersensitivity reaction [15,30,35–39]. These protocols need hospitalization of the patient and are usually complicated and time consuming. Rapid desensitization has also been attempted to achieve temporary tolerance within a relatively short period of time (typically 4–8 h) [26]. Its cellular and molecular mechanism is not fully understood. Recently, Castells *et al.* [40] presented a 12-step i.v. and intraperitoneal desensitization protocol suitable in hypersensitivity to various chemotherapeutic agents. Nevertheless, prolonged desensitization protocols, which may be more tolerable because it has been shown that the drug concentration rate in the extracellular fluid is an important factor [35]. Patients must be fully informed of the risks, as there is still danger of anaphylaxis in patients undergoing a trial of desensitization, as has already been described in some cases [41].

Carboplatin skin testing has been used to predict hypersensitivity reactions upon its readministration [2,35,42] but not widely because of the time, effort, and training that is necessary. In the Markman *et al.* [42] study, anaphylaxis occurred in six of seven patients who had a positive skin test and who were readministered carboplatin. They suggested that skin testing be used to predict hypersensitivity even before the first carboplatin administration, as a negative test was associated with a substantially decreased incidence of severe allergic reactions. In the Zanotti *et al.* study [2], which was based on patients with recurrent ovarian or peritoneal carcinoma, 28% of the patients had positive IDs and were not retreated with carboplatin. Skin testing is positive in over 80% of reactive patients [2,26]. When skin tests are negative, the risk of hypersensitivity reactions is reduced almost seven-fold or even eliminated [2]. Desensitization seems to reverse skin test positivity [35].

Another option available, which allows continuation of platinum-based chemotherapy, is the administration of a different platinum salt without additional desensitization [12,19,43–46]. However, the incidence of cross-allerginicity between platinum compounds is not known. Although studies in women with gynecological malignancies have shown no general cross-reactivity to cisplatin after carboplatin hypersensitivity reactions, deaths have been reported in other studies [31,32], highlighting the role of skin testing in excluding potential cross-reactivity. Skin testing has rarely been used in this specific setting. [47,48] In the three cases presented in our report, the patients tested negative for cross-reaction and were able to continue treatment with a different platinum agent. In all three cases, skin testing allowed safe continuation of platinum-based treatment in platinum-sensitive patients without pretreatment and the need for high-dose steroid treatment. This can also be useful in patients with poor glucose control and relative contraindications to prolonged steroid exposure [31]. During carboplatin–cisplatin substitution, efforts should be made to avoid the additional risk of neurotoxicity [49].

Conclusion

In the case of carboplatin hypersensitivity, administration of cisplatin is a reasonable option to continue platinum-based chemotherapy. Considering that there have been two deaths reported upon cisplatin administration in patients allergic to carboplatin [31,32], skin testing with cisplatin before the administration can help identify the patients with low risk of cross-sensitivity reaction, which can allow safe administration of cisplatin without the need of extended steroid premedication. Owing to the great increase in the incidence of hypersensitivity reaction after multiple doses of carboplatin, it is also recommended that skin testing be performed in every patient before administering the eighth dose of this drug.

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