

CLINICAL CASES

Anaphylactoid reaction to carboplatin: successful “desensitization”

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ABSTRACT

Carboplatin (CP) hypersensitivity reactions have been reported in nearly 12% of patients treated with this drug. The pathophysiologic mechanisms of these reactions have not been entirely elucidated. Various hypotheses are under discussion. CP hypersensitivity reactions could be IgE-mediated, caused by low-molecular platinum compounds acting as haptens. Platinum salts are also able to release histamine from basophils and mast cells, and some events seem to be non-immune-mediated direct histamine release. We report a case of CP tolerance induction in a 65-year-old man. During the third course of CP he experienced an anaphylactic reaction. Skin testing was negative. Suspecting the possibility of an anaphylactoid reaction due to histamine release, we developed a protocol to induce tolerance. Pre-medication with corticosteroid and antihistaminic was performed before intravenous CP infusion. The bag with CP was first infused 60 ml/h for 30 minutes; the infusion was well tolerated and infusion was continued at 100 ml/h for the next 60 minutes and thereafter at 120 ml/h until the bag was finished. Following this “desensitization”, monthly courses of CP using the same protocol have been well tolerated.

Key words: Platinum salts. Carboplatin. Hypersensitivity. Anaphylactoid reaction. Anaphylaxis. Drug allergy. Desensitization. Tolerance induction.

RESUMEN

En cerca del 12% de los pacientes tratados con carboplatino (CP) se han descrito reacciones de hipersensibilidad a este fármaco. Los mecanismos patofisiológicos de estas reacciones no se han esclarecido del todo, y se barajan varias hipótesis. Las reacciones de hipersensibilidad a la CP podrían ser mediadas por la IgE, o provocadas por compuestos de platino de bajo peso molecular que actúen como haptenos. Las sales de platino son asimismo capaces de liberar histamina de los basófilos y mastocitos, y algunas reacciones parecen proceder de una liberación directa de histamina no inmunomediada. Se expone el caso de una inducción de tolerancia a la CP en un varón de 65 años. Durante el 3.º tratamiento con CP, el paciente experimentó una reacción anafiláctica. La prueba cutánea resultó negativa. Pensando en la posibilidad de una reacción anafilactoide debida a la liberación de histamina, desarrollamos un protocolo para inducir la tolerancia. Se realizó una premedicación con corticosteroides y antihistamínicos previa a la infusión intravenosa de CP. La primera infusión con una bolsa de CP se realizó a 60 ml/h durante 30 minutos; la infusión fue bien tolerada y procedimos a administrar 100 ml/h durante 60 minutos más, para después pasar a 120 ml/h hasta terminar la bolsa. Los ciclos mensuales con CP han sido bien tolerados tras esta “de-

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sensibilización” mediante la aplicación del mismo protocolo.

Palabras clave: Compuestos de platino. Carboplatino. Hipersensibilidad. Reacción anafiláctica. Anafilaxia. Alergia medicamentosa. Desensibilización. Inducción de tolerancia.

INTRODUCTION

Carboplatin (CP) has been demonstrated to be one of the most useful and well-tolerated cytotoxic agents available for a wide variety of malignancies. It is a platinum-containing chemotherapeutic agent that was developed to minimize the toxicities of cisplatin. As a result of its extended use, an increased incidence of carboplatin-associated hypersensitivity reactions has been observed¹⁻³. CP hypersensitivity reactions have been reported in nearly 12% of patients treated with this drug¹. The pathophysiologic mechanisms of these reactions have not been entirely elucidated¹⁻⁸. Previous reports found a dramatic increase of hypersensitivity reactions in patients receiving several courses of the drug¹. A 1% incidence of hypersensitivity reactions was reported in patients receiving less than 6 courses of the agent; however, this rate increased to 27% in patients intaking more than 7 courses of the drug. The median number of platinum courses for the first hypersensitivity reaction was 8. In these reactions, greater than 50% of patients show moderately severe symptoms, including erythroderma, tachycardia, angina, wheezing, urticaria, facial angioedema, dyspnea, hypertension, or hypotension¹. A growing number of reports have described life-threatening reactions and even death due to CP hypersensitivity reactions^{1,3-8}. Different hypotheses are under discussion. These hypersensitivity reactions could be caused by low-molecular platinum compounds acting as haptens^{3,9,10}; however for CP, haptenic properties have not been unequivocally demonstrated. Skin tests have been performed with positive results in some occasions^{2-5,11}. Platinum salts are able to release histamine from basophils and mast cells³, and some events seemed to be non-immune-mediated direct histamine release⁷. Re-challenge and desensitization protocols have been used in these reactions^{1,2,4,6-11}. The following is the case of an anaphylactoid reaction due to CP with a successful desensitisation.

CASE REPORT

The following is a case dealing with a protocol of CP tolerance induction in a 65-year-old man with a urinary carcinoma with extensive pelvic involvement. He had previously received 2 courses with methotrexate, vimblastin and CP as palliative chemotherapy without problems. Ondasetron and 125 mg of 6-alpha-methyl-prednisolone were employed usually as pre-treatment. During the 3rd course of CP he experienced intense and generalised pruritus with facial angioedema, palmar erythema, anxiety, dyspnoea and hypotension (80/40 mmHg) approximately 10 minutes after initiation of CP infusion. No other cytostatic drug has been previously administered this day. Intravenous administration of CP was discontinued and the patient was treated with oxygen, intravenous fluids, 300 mg of hydrocortisone and 5 mg of intravenous dexchlorpheniramine. Symptoms subsided in 30 minutes and blood pressure returned to normal after 90 minutes.

Skin Prick testing and intradermal testing with ondasetron and CP were negative.

Thinking on the possibility of an anaphylactoid reaction due to histamine release we developed a protocol to induce CP tolerance. Pre-medication with oral prednisone (50 mg), ranitidine (150 mg) and dexchlorpheniramine (6 mg) was performed 12, 6 and 1 hour before intravenous infusion of CP. Also, hydrocortisone (200 mg) was intravenously injected at the beginning of the CP infusion. Oncologists in this patient indicated a total dose of 250 mg of CP. The 250 mg of CP were diluted in 250 ml of D5W (concentration 1 mg/mL). The bag was first infused 60 mL/h during 30 minutes; the infusion was well tolerated and we went on infusing at 100 mL/h for next 60 minutes, and after that, at 120 mL/h to finish the bag. A total of 150 minutes was spent in the protocol. No hypersensitivity symptoms were developed. Monthly courses of CP have been well tolerated after the “desensitisation”, employing the same protocol.

DISCUSSION

Hypersensitivity to platinum compounds is well known among refinery workers inhaling complex salts of platinum^{9,10}. These clinical manifestations have been considered as a type 1 hypersensitivity¹⁰.

CP has been demonstrated to be one of the most useful and well-tolerated cytotoxic agents available in those patients with urinary and gynaecologic cancers. There are conflicting reports in the literature about the mechanism of CP hypersensitivity reac-

tions. Several reports describe the use of skin testing in individuals sensitised by platinum compounds. Typical wheal and flare responses to intradermal injections of commercially available CP preparations occurred patients who had previously suffered hypersensitivity reactions to CP^{2,6,11}. A reasonable negative predictive value is also suggested in several reports which do not describe any reaction to skin testing in CP-exposed, but non sensitised, individuals^{2,3,6,11}. A specific mechanism for CP hypersensitivity reactions is suggested by the finding that almost 50 % of all such episodes in the biggest analysed group, occurred during course 8th of CP-based therapy¹. That fact could be caused by low-molecular platinum compounds acting as haptens³, although for CP, haptenic properties have not been unequivocal demonstrated. However, Platinum salts are also able to release histamine from basophils and mast cells³, and some events seemed to be non-immune-mediated direct histamine release⁷.

Re-challenge and desensitisation protocols have been used in many cases^{1,2,4,6-8,11}. In a report, administering CP only to patients with a negative skin test reduced the incidence of hypersensitivity reactions nearly seven-fold and possibly eliminate the occurrence of severe reactions altogether. Patients demonstrating a positive skin test seem to have a high probability of being sensitised to CP. Some patients tolerated cross-over to cisplatin therapy without hypersensitivity symptoms³.

For patients with a positive skin test, one must carefully weigh the risks and benefits of continuation of CP therapy. In our case, the negativity of the skin testing and the reaction in the 3rd course point out a non-IgE-mediated mechanism. An attempt to

“desensitize” the patient or provide a maximum immunologic blockade (as in our case) is probably justified in specific patients, mainly if they have negative skin tests, according to oncology clinical setting in each case. The good tolerance after slow rate of CP infusion in our patient confirms the non-IgE-mediated mechanism.

REFERENCES

1. Markman M, Kennedy A, Webster K, Elson P, Paterson G, Kulp B, Belinson J. Clinical features of hypersensitivity to carboplatin. *J Clin Oncol* 1999;17:1141-5.
2. Windom HH, McGuire III WP, Hamilton RG, Adkinson Jr. NF. Anaphylaxis to carboplatin-a new platinum chemotherapeutic agent. *J Allergy Clin Immunol* 1992;90:681-3.
3. Weidmann B, Mülleneisen N, Bojko P, Niederle N. Hypersensitivity reactions to carboplatin. Report of two patients, review of the literature, and discussion of diagnostic procedures and management. *Cáncer* 1994;73:2218-22.
4. Goldberg A, Confino-Cohen R, Fishman A, Beyth Y, Altaras M. A modified prolonged desensitization protocol in carboplatin allergy. *J Allergy Clin Immunol* 1996;98:841-3.
5. Menczer J, Barda G, Glezerman M, Hyat H, Brenner Y, Brickman CM, Tani A. Hypersensitivity reaction to carboplatin. Results of skin tests. *Eur J Gynaecol Oncol* 1999;20:214-6.
6. Broome CB, Schiff RI, Friedman HS. Successful desensitization to carboplatin in patients with systemic hypersensitivity reactions. *Med Pediatr Oncol* 1996;26:105-10.
7. Kook H, Kim KM, Choi SH, Choi BS, Kim HJ, Chung SY, Choi SJN, Hwang TJ. Life-threatening carboplatin hypersensitivity during conditioning for autologous PBSC transplantation: successful rechallenge after desensitization. *Bone Marrow Transplant* 1988;21:727-9.
8. Sims-McCallum RP. Outpatient carboplatin desensitization in a pediatric patient with bilateral optic glioma. *Ann Pharmacother* 2000;34:477-8.
9. Cleare MJ, Highes EG, Jacoby B, et al. Immediate (type I) allergic responses to platinum compounds. *Clin Allergy* 1976; 6:183-95.
10. Ørbaek P. Allergy to the complex salts of platinum: A review of the literature and three case reports. *Sand J Work Environ Health* 1982;8:141-5.
11. Zanolini KM, Rybicki LA, Kennedy AW, Belinson JL, Webster KD, Kulp B, Peterson G, Markman M. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001;19:3126-9.