Case Report

Diagnosis and Management of Hypersensitivity Reactions Caused by Oxaliplatin

T Herrero,[1] P Tornero,[1] S Infante,[1] V Fuentes,[1] MN Sánchez,[2] M De Barrio,[1] ML Baeza[1]

[1]Allergy and [2]Pharmacology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Abstract. Hypersensitivity reactions to oxaliplatin have been increasing since its introduction at the end of the 1990s, but allergy tests with antineoplastic drugs are rarely used to aid diagnosis. We describe 5 cases in which hypersensitivity reactions to oxaliplatin after several courses of chemotherapy were managed by allergy testing and desensitization. Skin prick tests were negative at 1 mg/mL in all patients, positive at 10 mg/mL in 2 tested patients, and negative in 10 control subjects. Intradermal tests were positive and not irritant at 0.01 to 0.001 mg/mL concentrations. A desensitization protocol with increasing concentrations and flow rates was successfully completed in all patients. We conclude that prick and intradermal skin tests are useful in the diagnosis of hypersensitivity reactions to oxaliplatin and that the desensitization protocol performed avoided discontinuation of chemotherapy in all patients.

Key words: Desensitization. Hypersensitivity reactions. Oxaliplatin. Platinum analogs.

Resumen. Las reacciones de hipersensibilidad a oxaliplatino, han aumentado de forma progresiva desde finales de 1990. Sin embargo, los estudios alergológicos realizados con citostáticos, rara vez han servido de ayuda en el diagnóstico de las reacciones de hipersensibilidad. Describimos 5 pacientes que, después de varios ciclos de quimioterapia presentaron reacciones de hipersensibilidad por oxaliplatino, fueron diagnosticados con pruebas alergológicas y tratados con pautas de desensibilización. Las pruebas cutáneas en prick a 1mg/ mL fueron negativas en todos los pacientes, a 10mg/mL fueron positivas en 2 pacientes testados, y negativas en 10 controles. La intradermorreacción fue positiva y no irritante entre 0.01 y 0.001 mg/mL. Todos lo pacientes completaron con éxito un protocolo de desensibilización a concentraciones y velocidad de perfusión progresivamente crecientes. Concluímos que las pruebas cutáneas en prick e intradermorreacción son útiles en el diagnóstico de las reacciones de hipersensibilidad por oxaliplatino y que el protocolo de desensibilización utilizado evitó el abandono del tratamiento en todos los pacientes.

Palabras clave: Desensibilización. Reacciones de hipersensibilidad. Oxaliplatino. Análogos de platino

Introduction

Hypersensitivity reactions are increasingly common among adverse effects reported for antineoplastic drugs. These reactions raise important questions about diagnosis and therapeutic management of the patient. There is confusion about the exact mechanism involved in their etiology. Cancer patients need to continue treatment because the drug causing the reaction is commonly the most effective one for their disease.

Oxaliplatin (*trans*-L, 1,2 diamino-cyclohexane oxaliplatinum, or L-OHP) is a third generation platinum salt. Its efficacy in combination with fluorouracil (5-FU) and leucovorin has been demonstrated in patients with colorectal carcinoma. The most characteristic and dose-limiting toxic effect of L-OHP is sensory neuropathy. Nausea, vomiting, diarrhea, and hematologic dyscrasias are also fairly frequent adverse reactions. Since its introduction, hypersensitivity reactions such as urticaria, angioedema, anaphylaxis, fever, wheezing, and cutaneous

rash have been described in sporadic treatment courses [1-3].

Cross-reactivity between oxaliplatin and other platinum analogs carboplatin (CBDCA) and cisplatin (CDDP) are rarely found [4], maybe because their oxaliplatin ligand, 1,2 diamino-cyclohexane, is rather different.

We describe our experience in 5 patients who suffered hypersensitivity reactions with L-OHP. We detail the allergy tests and the adapted desensitization schedule which enabled us to complete the remaining chemotherapy cycles.

Description of Cases

Patients

Case 1: A 58-year-old nonatopic male with no previous episodes of drug allergy was diagnosed with metastatic colorectal carcinoma. He received L-OHP, 5-FU and leucovorin, and ondansetron. During the third course of treatment he developed an erythematous and pruritic cutaneous rash, facial edema, hoarseness and dysphagia, 1 hour after beginning the L-OHP perfusion (78 mg/m^2).

Case 2: A 40-year-old female with a previous adverse reaction to iodine contrast media was diagnosed with colorectal carcinoma. She received treatment with L-OHP, 5-FU, leucovorin, and granisetron. During the L-OHP perfusion of the fifth course, 60 minutes after the start (82 mg/m^2) she presented itching hives on trunk and thighs.

Case 3: A 71-year-old female was diagnosed with gastric carcinoma. She had received chemotherapy with L-OHP, 5-FU, leucovorin, and granisetron. Thirty minutes after the start of L-OHP perfusion during the sixth course (57 mg/m^2), she suffered generalized erythema and severe itching on hands. She had reported similar but much milder symptoms during the previous cycle.

Case 4: A 69-year-old nonatopic male with no previous drug allergic reactions diagnosed with colorectal carcinoma in 1997 was treated with several courses of raltitrexed followed by 5-FU and leucovorin. He received cycles of L-OHP, 5-FU, and leucovorin which were well tolerated in 1998, and with irinotecan in 2000. A year later, 24 hours after the second infusion of L-OHP, 5-FU, leucovorin, and granisetron, he presented itching facial erythema, and fever. Later, he tolerated 2 more cycles, but 10 minutes after the beginning of the L-OHP perfusion in the fifth course (85 mg/m^2), he suffered pruritus on palms and soles, followed by discomfort, generalized heat and red-violaceous erythema.

Case 5: A 42-year-old male with previous adverse reactions to iodine contrast media and penicillin anaphylaxis was diagnosed with colorectal carcinoma. He received chemotherapy with L-OHP, 5-FU, and leucovorin. During the fifth course, 5 minutes after beginning the L-OHP perfusion (85 mg/m^2), he experienced pruritus on palms and head followed by facial urticaria and edema.

Reactions in all patients occurred between the third and sixth cycles of therapy, 5 to 60 minutes after beginning the L-OHP perfusion. Thereafter, all patients tolerated 5-FU and leucovorin.

Allergy Tests and Desensitization

Skin tests and controlled challenges with the antiemetic drugs (ondansetron and granisetron) were performed. Skin prick tests were performed with 0.1 and 1 mg/mL of L-OHP in the first 3 patients, and at 10 mg/mL in the patients 4 and 5. Intradermal tests were performed with concentrations of 0.001, 0.01, 0.1, and 1mg/mL in saline solution. Tests at these concentrations were negative in 10 control subjects who had previously been treated with L-OHP.

The L-OHP administration started at a flow rate of 0.003 mg/min (0.01mg/mL), with increasing doses every 30 to 60 minutes until 0.75 mg/min (0.18 mg/mL) was reached. The whole protocol lasted for 5 to 6 hours and was carried out as follows: a) no pre-treatment was administered in order to avoid concealing early signs of anaphylaxis; b) all patients were monitored and close medical supervision was maintained; c) the flow rate or drug concentration which had produced the reaction was never reached [5, 6]; d) the protocol was slightly individualized based on the concentration and flow rate appropriate for each patient; and e) all patients signed an informed consent statement.

Outcomes

Skin tests and controlled challenge to the antiemetic drugs were negative in all patients. The skin prick tests to L-OHP at 1mg/mL in the first 3 patients were negative, but patients 4 and 5 had the positive reactions to the test done at 10 mg/mL. All patients were positive to intradermal tests at 0.01 mg/mL. Patient 3 was also positive with 0.001 mg/mL.

The desensitization protocol was successful in all patients. Patients 1, 2, 3, and 4 had no reaction during the perfusion and tolerated the remaining L-OHP courses (1 course for patients 1, 2 and 4, and 2 for patient 3).

During the first desensitization protocol (0.04 mg/mL of L-OHP at 0.16 mg/min), patient 5 developed pruritus on soles and palms. The perfusion was stopped and he was treated with dexchlorpheniramine. The symptoms disappeared in 15 minutes and the desensitization protocol was resumed at 0.08 mg/min. The last dose (40 mg) was administered at 0.16 mg/mL with good tolerance. The total dose was reached after 11 hours.

Patient 5 received two more courses without problems and the prick test turned negative. At the end of fourth

cycle, he developed a fever of 39 °C, profuse sweating, erythema, cough, and eyelids edema. The treatment was discontinued and a new line of chemotherapy was followed. Two years later, due to therapeutic failure of that new line of chemotherapy, L-OHP was again prescribed. Skin tests had turned negative and two more courses of L-OHP were well tolerated following the last individualized protocol.

Discussion

The first reference to platinum salts reaction appeared in 1945 [7], described as a risk factor for occupational asthma in platinum-refinery workers. Since 1970, the year CDDP emerged as an antineoplastic agent, several hypersensitivity reactions with this drug have been reported. These reactions ranged from mild cutaneous rash to severe anaphylaxis, with an incidence of 5% to 20% [8, 9], and some years later evidence of similar reactions to CBDCA became available [5, 6, 10].

Since its introduction at the late 90's, L-OHP hypersensitivity reactions have been reported increasingly. Currently, L-OHP is a first line drug in the treatment of colorectal carcinoma.

Meyer et al [4] and Brandi et al [11] estimated the incidence of hypersensitivity reactions to L-OHP at around 12% to 13%. The nature of the symptoms and the positive skin tests to this drug [4, 11] supported an IgE-mediated mechanism. This hypothesis is defended by a large number of authors [4, 11,12], but this mechanism has not been confirmed and the nature of the reaction is still debated. It has also been suggested that L-OHP acts as a superantigen, causing lymphocyte over-activation and massive cytokine release; superantigens stimulate T-cell proliferation and cytokine production by direct binding to major histocompatibility complex class II molecules on antigen-presenting cells with subsequent stimulation of T cells [13]. In our opinion the reactions experienced by these patients were IgE mediated. This is supported by the following data: the symptoms were consistent with allergic reactions, the reactions appeared after several courses of therapy, the symptoms began in the first 60 minutes of the perfusion with small amounts of the drug, and all had positive skin tests.

Some authors have reported positive intradermal tests to L-OHP [4] but prick test positivity at 1 mg/mL has never been reported. The use of a 10 mg/mL concentration gave a positive cutaneous reaction in the 2 tested patients and did not elicit irritant responses in the control subjects. This seemed relevant to diagnosis. The positivity of the skin tests should establish a strong basis for managing these patients by carrying out a desensitization protocol.

Working-up desensitization protocols, with increasing concentrations and flow rate, have permitted us to complete the treatment in all patients. Similar protocols have been employed by other authors [4] with CDDP and CBDCA [6,14,15], following the same guidelines as in other traditional drugs.

We would like to emphasize the case of patient 5 because it brings together many common features of desensitization protocols. He had a mild reaction during the first perfusion which reversed with antihistamines allowing continuation of the treatment at a lower concentration and rate. Two more cycles were well tolerated, turning the prick tests negative. During the fourth cycle, an hour after ending L-OHP perfusion, he developed cough, erythema, eyelids edema, and fever. Finally, 2 years later, he underwent L-OHP chemotherapy again. At that moment skin tests had become negative, probably because of immunological memory loss, and he tolerated 2 more courses with this drug.

In conclusion, we highlight the usefulness of skin tests as a diagnostic test for L-OHP allergy and the usefulness of a desensitization protocol in avoiding withdrawal of a very important therapy.

References

1. Tournigand C, Maindrault-Goebel F, Louvet C, De Gramont A, Krulik M. Severe anaphylactic reactions to oxaliplatin. Eur J Cancer. 1998;34:1297-98.
2. Larzilliere I, Brandissou S, Breton P, Lingoungou A, Cargot D, Ramain JP, Harnois C. Anaphylactic reaction to oxaliplatin: a case report. Am J Gastroenterol. 1999;94: 3387-8.
3. Medioni J, Coulon MA, Morere JF, Hennebelle F, Piperno-Neumann S, Breau JL. Anaphylaxis after oxaliplatin. Ann Oncol. 1999;10:610.
4. Meyer L, Zuberbier T, Worm M, Oettle H, Riesse H. Hypersensivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. J Clin Oncol. 2002;20:1146-7.
5. Windom HH, Mcguire WP, Hamilton RG, Adkinson NF. Anaphylaxis to carboplatin- a new platinum chemotherapeutic agent. J Allergy Clin Immunol 1992;90:681-3.
6. Goldberg A, Confino-Cohen R, Fihman A, Beyth Y, Altaras M. A modified, prolonged desensitization protocol in carboplatin allergy. J Allergy Clin Immunol. 1996;98:841-3.
7. Hunter D, Milton R, Perry KMA. Asthma caused by complex salts of platinum. Br J Ind Med. 1945;2:92-8.
8. Cleare MJ, Hughes EG, Jacob B, Pepys B. Inmediate (type I) allergic responses to platinum compounds. Clin Allergy. 1976;6:183-95.
9. Shlebak AA, Clark PI, Green JA. Hypersensitivity and cross reactivity to cisplatin and analogues. Cancer Chemother Pharmacol. 1995;35:349-51.
10. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, Belison J. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol. 1999;17:1141-5.
11. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, DI Marco MC, Biasco G. Hypersensitivity reactions related to oxaliplatin. British Journal of Cancer. 2003;89(3):477-81.
12. Dold F, Hoey D, Carberry M, Musket A, Friedberg V; Mitchell E. Hypersensitivity in patients with metastasis colorectal carcinoma undergoing chemotherapy with oxaliplatin. Proc Am Soc Clin Oncol. 2002;38:21.

13. Tonini G, Santini D, Vincenzi B, Borzomati D, Dicuonzo G, La Cesa A, Onori N, Coppola R. Oxaliplatin may induce cytokine-release syndrome in colorrectal cancer patients. J Biol Regul Homeost Agents. 2002;16:05-9.
14. Broome CB, Schiff RI, Friedman H. Succesful desensitization to carboplatin in patients with systemic hypersensitivity reactions. Medical and Pediatric Oncology. 1996;26:105-10.
15. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-12-step protocol effective in 35 desensitizations in patients with gynaecological malignancies and mast cell/IgE-mediated reactions Gynecol Oncol. 2004;95:370-6.

Teresa Herrero

Servicio de Alergia
H.G.U. Gregorio Marañón
Dr. Esquerdo, 46
28007 Madrid, Spain
E-mail: therrero@ya.com