

Effectiveness of oxaliplatin desensitization protocols

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Received: 8 March 2012 / Accepted: 28 May 2012
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Abstract

Introduction Hypersensitivity reaction (HSR) to antineoplastic drugs can force doctors to stop treatment and seek other alternatives. These alternatives may be less effective, not as well tolerated and/or more expensive. Another option is to use desensitization protocols that induce a temporary state of tolerance by gradually administering small quantities of the antineoplastic drug until the therapeutic dosage is reached. The aim of this study is to assess the effectiveness of oxaliplatin desensitization protocols.

Materials and methods A retrospective observational study was carried out between January 2006 and May 2011. The inclusion criteria were patients undergoing chemotherapy treatment with oxaliplatin who had developed an HSR to the drug and who were candidates for continuing the treatment using a desensitization protocol. The patients' clinical records were reviewed and variables were gathered relating to the patient, the treatment, the HSR, and the desensitization protocol administered. The

data were analysed using version 18.0 of the statistics program SPSS.

Results A total of 53 desensitization protocols were administered to 21 patients. In 89 % of these cases, no new reactions occurred while the drug was being administered. New reactions of mild severity only occurred in 11 % of cases, and none of these reactions were severe enough for treatment to be stopped. All patients were able to complete the desensitization protocol.

Conclusion This study confirms that oxaliplatin desensitization protocols are safe and effective and allow patients to continue with the treatment that initially caused an HSR.

Keywords Oxaliplatin · Desensitization · Hypersensitivity reactions

Introduction

All chemotherapy drugs have the potential to cause a hypersensitivity reaction (HSR), but certain groups have been associated with a higher risk. These include platinum-based drugs (cisplatin, carboplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), asparaginases, monoclonal antibodies and epipodophyllotoxins.

The incidence of HSR to oxaliplatin ranges between 12 and 15 %, although these reactions are only severe (type 3–4) in 0.5–2 % of cases. As the use of this chemotherapy drug is gradually increasing, the incidence of HSR is also likely to increase [1–3].

The clinical manifestations of HSR to oxaliplatin include erythema, itchiness, rash, flushing, heart rate and blood pressure changes, nausea, fever, edema/angio-edema, shortness of breath and bronchial spasms. Rare cases of anaphylaxis and death have also been reported [4, 5].

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Symptoms of HSR can appear as soon as the drug infusion starts, during the infusion, or even after the treatment has been fully administered. There have been some cases of delayed HSR to oxaliplatin, where symptoms began between 10 and 20 h after the drug infusion finished [6, 7], and generally after between 7 and 9 treatment cycles [8, 9].

A number of studies have analysed the risk factors that contribute to the development of HSR to oxaliplatin. One of the best-defined factors is the number of treatment cycles received. The incidence of HSR increases as the number of cycles increases, and most studies have found that patients receive an average of between seven and ten cycles before an HSR develops. High doses of the drug have also been associated with a higher risk of developing an HSR, as well as cases where patients receive oxaliplatin as a second line chemotherapy treatment or retreatment after a drug-free period [10–12].

Oxaliplatin HSR is diagnosed based on data from patients' clinical records and through skin tests. To assess HSR correctly, it is vitally important to write down a clinical description of the reaction when it first appears, as well as a chronology of the reaction and its relationship with the drugs involved. There are two methods for carrying out skin tests: a prick test and an intradermal test. Prick tests are less sensitive than intradermal tests, but they are safer as they very rarely cause any side effects. As such, prick tests are recommended as the initial test for IgE-mediated allergies, and intradermal tests are only used in cases where the prick test is negative but the clinical symptoms are highly suggestive of hypersensitivity.

Premedication with H1 antihistamines combined with corticosteroids is often used to try to prevent HSR or make them less severe. However, the benefit of using this premedication before administering platinum salts has not yet been proven and is a highly controversial practice. A number of authors, including Bhargava et al. [13] and Brandi et al. [14], say that it is not an effective way of preventing HSR. However, in their study, Kidera et al. [15] conclude that adding H1 and H2 antihistamines and increasing the corticosteroid dosage (dexamethasone 20 vs. dexamethasone 8 mg) during premedication in patients treated with Folfox from the sixth treatment cycle onwards significantly reduces the incidence of HSR. Another measure proposed to prevent the development of HSR to oxaliplatin is to decrease the speed of drug infusion, increasing administration time from 2 h to between 4 and 6 h.

Hypersensitivity reactions to antineoplastic drugs can force doctors to stop treatment and seek other alternatives. These alternatives may be less effective, not as well tolerated and/or more expensive. Another option is to use desensitization protocols that induce a temporary state of tolerance by gradually administering small quantities of the

antineoplastic drug causing the HSR until the therapeutic dosage is reached. The aim of this study is to assess the effectiveness of an oxaliplatin desensitization protocol. Effectiveness is measured based on the appearance (or lack thereof) of new HSR during the desensitization protocol or shortly after it is administered.

Materials and methods

Study design

A retrospective observational study was carried out in the Hospital Universitario 12 de Octubre in Madrid between January 2006 and May 2011.

The inclusion criteria were male and female patients aged 18 or over undergoing chemotherapy treatment with oxaliplatin who had developed an HSR to the drug and who had been referred to the Allergy Service as candidates for continuing the treatment using a desensitization protocol.

The information sources used were patients' oncology records and allergy records, treatment administration record from the oncology outpatient clinic, and prescription record from the electronic chemotherapy prescription program.

Variables related to the following were also gathered: the patient and his/her antineoplastic treatment, characteristics of the initial HSR, results of skin tests, and desensitization protocols administered.

The data were analysed using version 18.0 of the statistics program SPSS.

This research protocol was approved by the hospital's Ethics Committee.

All medical data obtained for the purposes of this study were strictly confidential. Any data that could allow patients to be identified were deleted from the database.

Classifying initial HSR

The HSR was classified based on their severity in accordance with the Common Toxicity Criteria version 3.0 (Table 1).

Skin tests

Skin tests were carried out to confirm the diagnosis of oxaliplatin hypersensitivity. Two types of skin test were carried out: prick tests and intradermal tests. The prick tests were carried out first. If the result of the prick test was negative, an intradermal test was carried out as well.

Both tests were carried out using standard solutions of oxaliplatin and 5 % glucose. The dilutions used were 0.01, 0.1, 1 and 5 mg/ml, starting with the most dilute and

Table 1 Grading of hypersensitivity reactions according to National Cancer Institute criteria (CTC v 3.0)

Grade	Hypersensitivity reactions
1	Transient flushing or rash Drug fever 38 °C (100.4 F)
2	Rash Flushing Urticaria Dyspnea Drug fever 38 °C (100.4 F)
3	Symptomatic bronchospasm with or without urticaria Parenteral medication or medications indicated Allergy-related edema/angioedema Hypotension
4	Anaphylaxis
5	Death

finishing with the least dilute. Saline solution was used as the negative control and histamine as the positive control.

The test results were read 15–20 min after they were carried out. In cases of delayed HSR, the tests were also read 24, 48 or 72 h later.

If the diameter of the wheal that developed was at least 3 mm longer than the wheal from the negative control, the result was considered to be positive.

Desensitization protocol

The desensitization protocols were administered by specialist staff from the hospital's Allergy Service. All patients

were informed and signed an informed consent form before the desensitization treatment started.

Table 2 shows an example of an oxaliplatin desensitization protocol for a dosage of 144 mg. The total oxaliplatin dosage is calculated by the oncologist based on the treatment regimen and the patient's biometric characteristics. This example is made up of 13 doses administered over a period of 3 h and 15 min, with a total volume of 800 ml of 5 % glucose. Initially, the doses are very small, and as the patient builds up a tolerance to the drug, the doses are gradually increased, usually doubling the dosage each time.

The desensitization protocol is administered intravenously, with the doses administered in accordance with the times specified in the protocol. The frequency of administration of the desensitization protocol will be specified in the patient's treatment plan.

All of the patients are premedicated with: corticosteroids: 1 mg/kg/day, ranitidine: 300 mg/day, cetirizine: 20 mg/day and montelukast: 10 mg/day. These drugs are administered the night before and 30 min before the desensitization protocol is administered.

Results

Patient characteristics

A total of 21 patients were included in the study, 15 women (71.4 %) and 6 men (28.6 %). All of these patients had developed an HSR to oxaliplatin but the decision was made to continue treatment with the drug using a desensitization protocol. The average age of the patients in the study group was 60.5. All of the patients in the study group had been

Table 2 Example of oxaliplatin desensitization protocol

Step number	Time (min)	Dose (mg)	Accumulative dose (mg)	Concentration (mg/ml)	Incidents	Volume of glucose 5 %
1	10	0.01	0.01	0.0002		50
2	10	0.025	0.035	0.0005		50
3	10	0.05	0.085	0.001		50
4	10	0.1	0.185	0.002		50
5	10	0.25	0.435	0.005		50
6	10	0.5	0.935	0.01		50
7	10	1	1.935	0.02		50
8	10	2	3.935	0.04		50
9	10	5	8.935	0.1		50
10	15	10	18.935	0.2		50
11	20	20	38.935	0.2		100
12	30	40	78.935	0.4		100
13	40	65	143.935	0.65		100
Total	195	144	143.935			800

diagnosed with colorectal cancer and 38 % had metastases in various different locations. 10 % had a history of drug, environmental or food allergies.

71 % of the patients were treated with Xelox (capecitabine plus oxaliplatin), 24 % with Folfox (fluorouracil plus oxaliplatin), and 5 % with Folfox and bevacizumab. The premedication administered for each treatment cycle was as per protocol: ondansetron 8 mg + dexamethasone 12 mg in 17 patients (81 %) and ondansetron 8 mg (without dexamethasone, as the patients were diabetic) in four patients (19 %).

15 patients (71 %) were undergoing first line chemotherapy treatment, while the remaining 6 (28.6 %) were undergoing second or third line treatment. Of these, three patients (14.3 %) were receiving a second round of treatment with oxaliplatin.

Characteristics of initial HSR

The patients in the study group developed the following symptoms of HSR to oxaliplatin: 81 % had skin symptoms (erythema, itchiness, hives, and in fewer cases rash and maculopapular lesions), 38 % had shortness of breath, 33 % hot flushes, 24 % bronchial spasms, 19 % edema/angio-edema, and 5 % hypotension. Based on their level of severity (Common Toxicity Criteria version 3.0.), 67 % of HSR were classified as grade 2 and 33 % as grade 3. No patients with a grade 4 HSR (severe) were considered to be candidates for desensitization. With regard to the time of onset of the HSR, 19 (90.5 %) appeared immediately (i.e. while the drug was being infused or during the hour immediately after the infusion was completed), and 2 (9.5 %) were delayed. HSR appeared, on average, after five cycles of oxaliplatin treatment. All of the HSR were resolved by administering symptomatic treatment: dexchlorpheniramine and intravenous corticosteroids. In some cases, oxygen and subcutaneous adrenaline were also required.

Attempts were made to restart the oxaliplatin treatment (without a desensitization protocol) after the HSR in just five patients (23.8 %). In all of these cases, the premedication administered was increased, and the oxaliplatin infusion time was increased. However, these attempts failed in all five patients, and the HSR reappeared with the same or worse symptoms as in the first reaction.

Results of the skin tests

Prick and intradermal skin tests were carried out on all the patients in the study group to confirm the diagnosis of oxaliplatin hypersensitivity. The results of the skin tests at the different concentrations are shown in Fig. 1. There was a low percentage of positive results, as the prick tests at 1

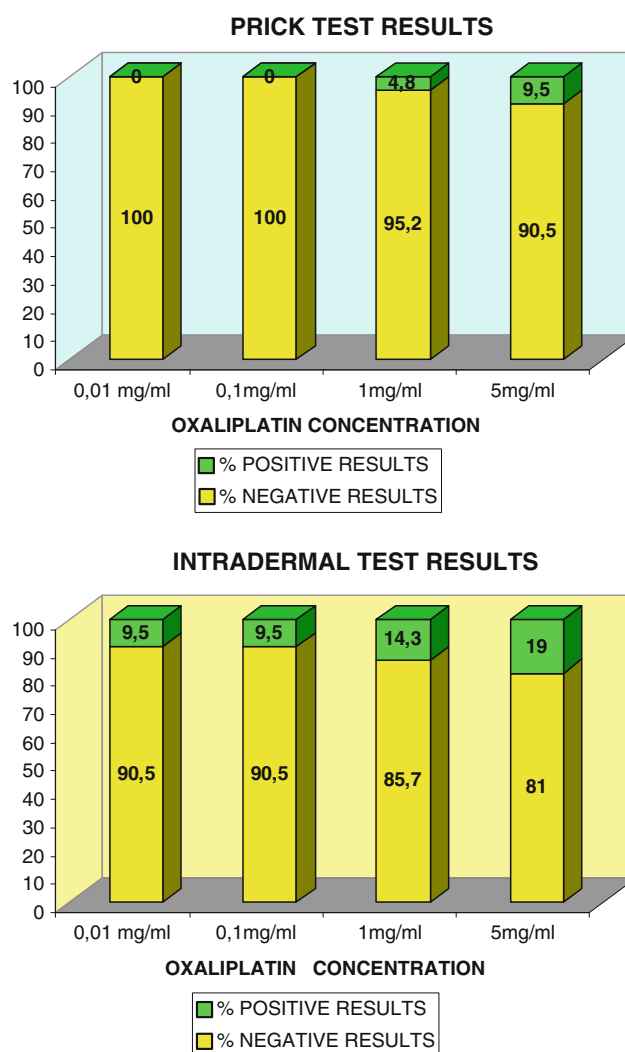


Fig. 1 Oxaliplatin skin test results

and 5 mg/ml were positive in just 4.8 and 9.5 % of patients, respectively. 9.5 % of intradermal tests at the lowest concentrations of 0.01 and 0.1 mg/ml were positive, while at the higher concentrations, 14.3 % were positive at 1 mg/ml and 19 % were positive at 5 mg/ml.

Desensitization protocols

A total of 53 desensitization protocols were administered to 21 patients during the study period, an average of two cycles per patient.

The protocols were made up of an average of 14 steps, were administered over a period of between 3 and 4 h, and the average volume administered was 850 ml. The total dosage administered for each protocol was the same amount prescribed to the patient before the HSR occurred.

New HSR occurred during six desensitization protocols (11 %), but there was no HSR in the remaining 47 (89 %). The six new HSR occurred in four of the patients (19 %),

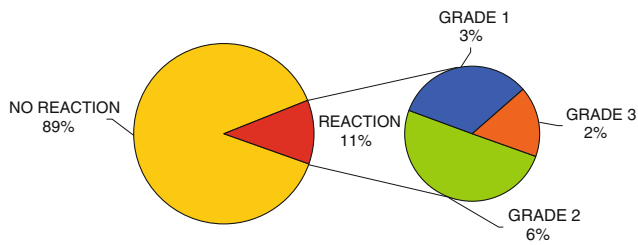


Fig. 2 Number and severity of reactions during desensitization

as two of the patients had a dual reaction. With regard to the severity of the new HSR, 50 % were grade 2, 33 % were grade 1, and 17 % were grade 3 (Fig. 2). Most of the symptoms of the HSR were found on the skin, with erythema, itchiness, hot flushes and rashes. In fewer cases, patients also complained of shortness of breath and/or edema. The new HSR that occurred during administration of the desensitization protocol was always of the same severity or less severe than the initial HSR. They were never more severe.

These new reactions occurred in the first desensitization cycles administered, and in the last steps of the desensitization process (3 in step 9, 1 in step 11, 1 in step 13 and another in step 14). Higher dosages are administered during these later steps.

The desensitization was completed and the whole therapeutic dosage administered in all patients, even those who experienced a new reaction.

The new HSR forced doctors to change the protocol for subsequent desensitization protocols, by lengthening the infusion time, in just one case (out of a total of six).

The measures taken to resolve these new HSR consisted of administering H1 antihistamines and intravenous corticosteroids. In two cases, oxygen also needed to be administered.

The desensitization protocol was not discontinued in any case as a result of safety concerns linked to the HSR caused by administration of the protocol. The main reasons for discontinuing the desensitization protocols were progression of the disease and neurological toxicity caused by the oxaliplatin.

Discussion

The pathophysiology of HSR to oxaliplatin is not yet fully understood. HSR occurs when patients have already received several treatment cycles and symptoms appear at an early stage of the infusion, and this suggests that IgE-mediated (Type I) sensitization must take place beforehand [2].

However, other authors have suggested that oxaliplatin could also cause hypersensitivity through other mechanisms. Maindault-Goebel et al. [16] described three cases

of type II hypersensitivity (through activation of complement and killer cells, developing immunological thrombopenia). Thomas et al. and Tonini et al. [17, 18] have postulated a super-antigen mechanism, resulting in the release of cytokines. In that sense, other paths to cytokine release induced by oxaliplatin have been reported and connected with side effects and antitumor activity. Ulrich-Pur et al. [19] described a correlation between fever in relation with oxaliplatin administration and release of IL-6, with the particularity that this side effect did not occur during the first cycle of therapy, suggesting a potential acquired or allergic form reaction. Wilson et al. [20] reported an increased transcription and secretion of IL-8 and its receptor by oxaliplatin with a potentiation of NF- κ B activation in androgen-independent prostate cancer cells, increasing the expression of antiapoptotic genes, results that supported NF- κ B activity as an important determinant of cancer cell sensitivity to oxaliplatin, and identified the induction of autocrine IL-8 receptor 2 signaling as a novel mode of resistance to this drug. This could be interesting for the future considering the appearance of new drugs able to block steps of these paths [21].

A total of 53 oxaliplatin desensitization protocols were administered throughout the study period, involving 21 patients. In 89 % of cases, no reactions occurred while the protocols were being administered. New reactions occurred during the desensitization protocol in just 4 patients (19 %), and in no cases did these new reactions lead to treatment being stopped.

These satisfactory results of oxaliplatin desensitization are consistent with the findings of other studies. For example, Edmondson et al. [22] describe a case in which a patient successfully underwent a total of 11 desensitization cycles. Bhargava et al. [13] report a patient who experienced a severe HSR to oxaliplatin but was successfully desensitized despite the severity of the reaction. Gammon et al. [23], Meyer et al. [24], and Castells et al. [25] describe more cases of successful desensitization to oxaliplatin which meant that treatment with the drug could be continued.

A number of studies have also been carried out with larger sample groups, including the studies by: Habert et al. [26] at the Paul Brousse Hospital in France, where 14 patients were desensitized and seven of them experienced a reaction while the protocol was being administered; Syrigou et al. [27] at the Sotiria General Hospital in Athens, where three patients were successfully desensitized; and Gottlieb et al. [28] at the DeKalb Medical Cancer Center, who obtained similar results, successfully desensitising three out of four patients. The fourth patient in this study received two infusions successfully but experienced a severe reaction during the third, forcing doctors to stop the treatment.

A number of studies have also been carried out in Spain, including works by: Herrero et al. [29] at the Gregorio Marañón Hospital in Madrid, in which five patients successfully completed the desensitization protocol so that treatment could continue—only one patient experienced symptoms while the treatment was being administered; and Gastaminza et al. [30] at the University Clinic in Navarre, where three patients were successfully desensitized. Although these studies had smaller sample groups, their results are similar to the findings of the analysis carried out here.

The reactions that occurred during the desensitization protocol were always of the same severity or less severe than the initial reaction, and they took place during the final stages of the treatment, when higher dosages were being administered. These results are consistent with the findings of Castells et al. [25], who analysed the safety of 413 desensitizations to different antineoplastic agents, and found that 82 % of reactions took place in the first two cycles of desensitization. They also concluded that the severity and frequency of the reactions both decreased in later desensitization cycles, and found that most reactions took place in the last step of the protocol.

In this study, desensitization was never stopped as a result of safety concerns linked to hypersensitivity. However, Gottlieb et al. [28] describe a case where the patient had such a severe HSR to oxaliplatin that the desensitization protocol had to be stopped.

The oxaliplatin hypersensitivity diagnosis was confirmed using skin tests: prick tests and intradermal tests. In this study, there was a low number of positive results using both tests. The intradermal skin test was found to be more sensitive than the prick test, as there was a higher percentage of positive results using this test at the same drug concentrations. The skin test results found by Gottlieb et al. [28] and Gastaminza et al. [30] were similar to the ones found here.

Therefore, the usefulness of skin tests in the diagnosis of the HSR to oxaliplatin is questionable, considering the signs and symptoms developed by the patient as the main diagnostic tool.

However, a lot of studies report a higher incidence of positive skin test results. For example, in the study by Garufi et al. [31], four out of five patients had positive intradermal skin tests, confirming the oxaliplatin hypersensitivity diagnosis in 80 % of the sample group. Similar results were obtained by Meyer et al. [24.] and Herrero et al. [29].

When considering the subjectivity of clinical diagnosis, other paths should be explored, especially those referred to molecular signatures. Some authors have investigated a gene expression profile that provides insights into pathways of oxaliplatin-related complications. In that sense, Rubbia-

Brandt et al. reported the results of a study directed to investigate the gene expression profile of 11 human livers with oxaliplatin-related veno-occlusive disease using microarrays techniques. The analysis of pathways showed major gene up regulation in six pathways including acute phase response (especially IL-6), coagulation system, oxidative stress and others. These authors concluded that oxaliplatin-related sinusoidal obstruction syndrome can be distinguished by a molecular signature. Similar applications should be considered in the future to determine molecular characteristics related to oxaliplatin HSR [32].

Conclusion

Desensitization protocols that administer the full therapeutic dose within 3–5 h are safe and effective in helping patients to build up a tolerance to the complete treatment. This provides a new option to allow patients to continue treatment with a drug which causes an HSR where there are no alternative treatments with the same level of effectiveness, or which they want to save for future lines of treatment.

The success of this therapy depends upon the minimum dosage at the start of the protocol, gradual dosage increases, and the time it takes to administer the drug.

However, it is important to note that the tolerance to the desensitized drug is only temporary, so if the patient needs to be given several treatment cycles the desensitization protocol will have to be carried out each time.

In all cases, the decision whether or not to carry out the desensitization process should be made by a multidisciplinary team, taking into account each patient's unique characteristics and weighing up the risks of a new reaction against the potential benefit of the treatment.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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