ORIGINAL ARTICLE

A New Rapid Desensitization Protocol for Chemotherapy Agents

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Abstract

Background: Desensitization has been used for some decades to treat patients with the allergenic drug when an alternative drug with similar efficacy and safety is not available. We present the results from a series of oncology patients desensitized at our hospital during the last 2 years.
Objective: To assess the efficacy of a new desensitization protocol in patients allergic to chemotherapy drugs.
Methods: We performed an observational retrospective study of 11 women (6 breast cancer and 5 ovarian cancer) who underwent our desensitization protocol. Four patients had immediate reactions to carboplatin, 3 to docetaxel, 3 to paclitaxel, and 1 to both docetaxel and paclitaxel. Premedication was administered in all cases. A 5-step protocol based on 5 different dilutions of the drugs was used.
Results: We performed 39 desensitization procedures: 14 to carboplatin, 3 to oxaliplatin, 16 to docetaxel, and 6 to paclitaxel. Eight patients tolerated the full dose in 36 procedures. One patient suffered an anaphylactic reaction to carboplatin that reverted with treatment. One patient had dyspnea after a paclitaxel cycle. One patient experienced dyspnea due to chronic pulmonary thromboembolism related to her disease.
Conclusion: Desensitization is a useful procedure in patients who are allergic to their chemotherapy agents.

Key words: Carboplatin. Chemotherapy agents. Desensitization. Hypersensitivity reactions. Paclitaxel.

Resumen

Antecedentes: La desensibilización con medicamentos es un procedimiento utilizado desde hace varias décadas que permite tratar a pacientes con el fármaco al que son alérgicos, cuando no existe un fármaco alternativo con similar perfil de eficacia y seguridad. Presentamos los resultados de los pacientes oncológicos desensibilizados en nuestro Hospital en los últimos dos años.
Objetivos: Comprobar la eficacia de un protocolo nuevo de desensibilización en pacientes alérgicos a citostáticos.
Métodos: Se trata de un estudio observacional retrospectivo. Once mujeres adultas (6 con cáncer de mama y 5 con cáncer de ovario) fueron tratadas mediante nuestro protocolo de desensibilización. Cuatro pacientes habían sufrido reacciones inmediatas previas con carboplatino, 3 con docetaxel, 3 con paclitaxel y 1 con ambos taxanos. Se administró premedicación en todos los casos. Se utilizó un protocolo en cinco pasos, utilizando 5 diluciones del fármaco a administrar.
Resultados: Se realizaron un total de 39 desensibilizaciones: 14 a carboplatino, 3 a oxaliplatino, 16 a docetaxel y 6 a paclitaxel. Ocho pacientes toleraron la dosis completa del fármaco en 36 desensibilizaciones. Una paciente sufrió una reacción anafiláctica a carboplatino que respondió al tratamiento. Una paciente padeció disnea tras un ciclo de paclitaxel. Una paciente sufrió disnea debido a un tromboembolismo venoso relacionado con su enfermedad.
Conclusión: La desensibilización es un procedimiento útil para agentes quimioterápicos en pacientes alérgicos.

Palabras clave: Carboplatino. Quimioterapia. Desensibilización. Reacciones de hipersensibilidad. Paclitaxel.

Introduction

Hypersensitivity reactions to taxanes and platins are not rare events. In the case of platins, these reactions are thought to be immunoglobulin (Ig) E–mediated, whereas taxanes elicit the release of mast cells and basophils. Hypersensitivity reactions to these drugs represent a challenge, because in some instances no alternative treatment is available. Consequently, the only option is to desensitize the patient to the chemotherapy agent.

Since the first desensitization protocol with drugs was described in a penicillin-allergic pregnant woman with syphilis, several empirical approaches have been developed [1]. They all involve suboptimal administration of the culprit drug followed by progressive dose increases. The mechanism through which tolerance is achieved is not known. Recent studies reported a role for certain molecules, such as the spleen tyrosine kinase gene [2] and the signal transducer and activator of transcription 6 gene [3].

In recent years, a significant number of desensitization procedures have been reported in patients receiving chemotherapy. Available data show that out of 413 desensitization procedures performed in 98 patients, 94% were well-tolerated or involved only mild reactions, with all patients being able to tolerate the full dose [4]. The total duration of the protocol used in these studies was 5 hours and 49 minutes.

The departments of Allergy, Oncology, and Pharmacy at our institution (Clinica Universidad de Navarra, Pamplona, Spain) collaborated to develop a desensitization protocol for taxanes and platins. Our aim was to administer the full dose in half the time of previously reported protocols. We report our results 3 years after implementing the protocol.

Methods

We performed an observational retrospective analysis of all patients who underwent desensitization protocols in 2006 and 2007.

Patients

Eleven women aged 30 to 74 years were included in the study. All the patients were receiving chemotherapy in our Oncology Department. Six patients had breast cancer and 5 had ovarian cancer. Four patients had reacted to carboplatin,

Table 1. Patient Characteristics

Patient	Age, y	Illness	Symptoms	Allergenic Drug	Number Cycles
1	57	Ovarian cancer	Dyspnea, chest pain, sickness	Carboplatin	5
2	30	Ovarian cancer	Dyspnea desaturation	Docetaxel Paclitaxel	1
3	74	Ovarian cancer	Palmar pruritus, facial rash, nausea	Carboplatin	9
4	35	Breast cancer	Genital pruritus, shivering, dyspnea	Paclitaxel	2
5	42	Ovarian cancer	Rash, pruritus, facial edema	Carboplatin	12
6	72	Breast cancer	Dyspnea, chest pain, sickness, loss of conscience	Docetaxel	1
7	51	Breast cancer	Facial edema, dysphagia, dyspnea	Docetaxel	1
8	59	Breast cancer	Facial edema, dysphagia, chest pain	Paclitaxel	5
9	38	Breast cancer	Dyspnea, cyanosis, facial rash, conjunctivitis	Docetaxel	1
10	64	Ovarian cancer	Palmoplantar pruritus, rash, abdominal pain, dyspnea, nausea	Carboplatin	8
11	58	Breast cancer	Dyspnea, laryngeal edema, rash, desaturation	Paclitaxel	2

3 to docetaxel, 3 to paclitaxel, and 1 to both docetaxel and paclitaxel. The individual features of the disease and reactions recorded during chemotherapy are summarized in Table 1. Depending upon the culprit drug, the reaction appeared at different stages of treatment. Carboplatin was associated with reactions between the fifth and twelfth chemotherapy cycle. Paclitaxel provoked a reaction during the first cycle in 1 patient and during the second cycle in 3 patients. Finally, in the case of docetaxel, all reactions were present during the first cycle.

Patients younger than 18 years were excluded. Before the protocol was administered, all patients gave their written informed consent after a complete oral and written explanation.

To be eligible to undergo the protocol, the patients must have suffered an immediate reaction within less than 1 hour after initiation of chemotherapy. Patients with a delayed drug reaction were excluded. We did not desensitize patients to whom an alternative drug with a similar efficacy profile could be administered.

We considered an allergic reaction to be a typical immediate hypersensitivity reaction involving cutaneous symptoms (urticaria with or without angioedema, flushing, itching), respiratory symptoms (shortness of breath, oxygen desaturation, cough, wheezing, chest tightness), cardiovascular symptoms (tachycardia, syncope, hypotension, hypertension), and gastrointestinal symptoms (nausea, vomiting, diarrhea). Patients who experienced atypical symptoms—shortness of breath, lumbar pain, or gastrointestinal symptoms, with no involvement of other systems—were excluded.

Diagnostic Procedures

We were unable to perform skin tests on all patients for logistic reasons (eg, timing and availability of chemotherapy agents). When they were performed, we used carboplatin (10 mg/mL for the prick test and 1 and 10 mg/mL for the intradermal test), oxaliplatin (5 mg/mL for the prick test and 0.5 and 5 mg/mL for the intradermal test), paclitaxel (0.6 mg/mL for the prick test and 0.06 mg/mL for the intradermal skin test), and docetaxel (0.4 mg/mL for the prick test and 0.04 mg/mL for the intradermal skin test).

We also performed the basophil activation test as described elsewhere [5]. Carboplatin and oxaliplatin were tested at a final concentration of 0.125 mg/mL and 0.03 mg/mL. Paclitaxel was tested at a final concentration of 0.0075 mg/mL and 0.0018 mg/mL, and docetaxel at a final concentration of 0.005 mg/mL and 0.00125 mg/mL.

Desensitization Protocol

The local ethics committee approved the protocol. Each patient underwent the first desensitization in the intensive care unit. Subsequent desensitizations were performed in an observation unit for close monitoring with 1 nurse for every 3 patients.

Premedication was administered in all cases and consisted of 60 mg of oral prednisone at 13 hours, 7 hours, and 1 hour before the procedure plus 5 mg of intravenous dexchlorpheniramine 1 hour before the procedure.

Drug Administration Procedure

Once the individual dose was calculated, we followed a rush protocol consisting of 5 drug delivery stages. An example of the protocol used in desensitization with carboplatin is summarized in Table 2. For the first 4 dilutions, the rate of intravenous administration was 150-200 mL/h; the last dilution was delivered at 280mL/h for carboplatin, 167 mL/h for oxaliplatin, 80 mL/h for paclitaxel, and 125 mL/h for docetaxel. Depending on the total dose and the drug, the procedure lasted from 2 to 5 hours.

Management of Adverse Reactions

If a mild reaction occurred, we suspended the infusion and administered 0.5 mg/kg of methylprednisolone. If the reaction involved respiratory symptoms, we also administered 5 mg of salbutamol nebulized over 5 minutes. Once the symptoms resolved, we continued with the procedure.

In cases of severe or moderate reaction, or when a mild reaction and the same symptoms appeared upon reinfusion, we started the infusion with the previous tolerated dose and rate.

Administration was only interrupted in cases of anaphylactic shock, for which epinephrine was injected.

Results

Skin tests were performed in 5 patients, 3 with taxanes and 2 with platins. We observed 1 isolated positive skin reaction with docetaxel.

We also performed the basophil activation test in 4 patients, 2 with taxanes and 2 with platins. All the results were negative.

We performed 39 desensitization protocols: 14 with carboplatin, 3 with oxaliplatin, 16 with docetaxel, and 6 with paclitaxel (Table 3).

Table 2. Desensitization Protocol for Carboplatin

	Volume, mL	Infusion Time, min	Time Accumulated	Dose Administered, mg	Cumulative Dose, mg
Solution A, 1/10000	50	15	15	0.03	0.03
Solution B, 1/1000	50	15	30	0.30	0.33
Solution C, 1/100	50	15	45	3.00	3.33
Solution D, 1/10	50	15	60	30.00	33.33
Solution E, 1/1	280	60	120	266.67	300.00

Table 3. Desensitization Protocols

Patient	Drug Sensitized	Number of Cycles Performed	Tolerance	Cutaneous Tests	BAT
1	Carboplatin Oxaliplatin	2 3	Yes	–	–
2	Paclitaxel Docetaxel	1 2	Dyspnea Yes	ND	ND
3	Carboplatin	2	Yes	ND	ND
4	Docetaxel	2	Yes	–	ND
5	Carboplatin	9	Yes	–	–
6	Docetaxel	4	Yes (chronic PTE)	ND	ND
7	Docetaxel	4	Yes	–	–
8	Paclitaxel	3	Yes	ND	ND
9	Docetaxel	4	Yes	Docetaxel, + Paclitaxel, –	–
10	Carboplatin	1	Anaphylaxis	ND	ND
11	Paclitaxel	2	Yes	ND	ND

Abbreviations: BAT, basophil activation test; ND, not done; PTE, pulmonary thromboembolism.

We were able to administer the full dose to all but 1 patient. Thirty minutes after the beginning of the last stage (approximately 352 mg of carboplatin) in the first desensitization, the patient developed grade II anaphylaxis with no cardiovascular symptoms that resolved 30 minutes after administration of methylprednisolone and dexchlorpheniramine.

Overall, 3 patients suffered an adverse reaction. One patient with hypersensitivity to docetaxel plus paclitaxel suffered from dyspnea with the last dose of paclitaxel; consequently, docetaxel was administered during the following 2 desensitizations without incident. After 4 desensitizations, 1 patient developed late shortness of breath due to chronic pulmonary thromboembolism associated with her disease. One patient suffered an anaphylactic reaction.

The remaining 8 patients tolerated the desensitization protocol without incident.

As for the efficacy of chemotherapy, tumor markers decreased after desensitization in 4 patients and increased in 5 (indicating disease progression). No data were available on tumor markers for 2 patients.

Discussion

Rapid desensitization protocols make it possible to administer treatment to patients who experience hypersensitivity reactions to chemotherapy agents such as taxanes [6], platins [7,8], and monoclonal antibodies [9]. We were able to achieve desensitization in all but 1 patient, even after shortening the protocol by more than 2 hours.

The patient who discontinued the protocol did so on the advice of her oncologist, who decided to try another drug for reasons of safety.

Our data show that desensitization protocols are not risk-free, and we do not have the means available to assess this risk. The case of cancer patients is particularly challenging, as chemotherapy is often the only way their disease can be controlled; consequently, more severe measures may be necessary to ensure drug delivery.

The adverse reactions we observed are consistent with the findings of other authors. Hypersensitivity reactions with platins usually appear when the patient has received more than 4-6 cycles, whereas taxanes produce reactions during the first or second chemotherapy cycle [4]. Consequently, the reaction is thought to be IgE-mediated in the case of platins. In fact, several authors recommend a positive skin test result as a predictor of future platin reactions [10]. Despite reports of a high incidence of positive skin test results with carboplatin [11], the 2 patients who suffered reactions to carboplatin in our study had negative results (in one of them the study was performed 1 year after she suffered the reaction). Studies must be performed to assess the specificity and sensitivity of skin tests to platins.

We investigated an in vitro marker of cell activation. However, we did not find any CD63 expression upon incubation of basophils with the chemotherapy agent involved. This might be because these reactions are mediated purely by mast cells or by the patient's immunodepressed state.

Our protocol differs from others applied in larger series [4], the main advantages being that our protocol is shorter and has fewer nursing care requirements. It also has fewer steps and, consequently, fewer administration errors. We used 5 different drug dilutions and the procedure was completed in 2 hours when well tolerated. Lee et al [7] used 3 dilutions

administered in twelve 15-minute steps, with a total duration of 5 hours and 49 minutes [7].

It is extremely useful to have different protocols in order to be able to choose approaches depending upon individual patient requirements. For instance, we think that the patient who developed an anaphylactic reaction could have tolerated the protocol of Lee et al [7]; however, as we mentioned above, it was impossible to assess this hypothesis, because her oncologist opted to change the treatment.

Nevertheless, protocols do not differ widely, since most of the drug is administered in the last step in all methods. Similarly, Lee et al [7] delivered 92% of the total dose in the last step within 3 hours. In our protocol, we administered 89% of the total drug dose in the last step in 1 hour. Thus, managing the pace of administration in this last step seems to play a key role in preventing adverse reactions. It would be interesting to compare the number of reactions between different approaches, since most occur during administration of the last doses [4].

The usefulness of premedication should also be borne in mind. This is a controversial issue. Some authors support avoiding it altogether [8], as early anaphylactic symptoms would be promptly recognized and treated. Other authors oppose this approach and recommend using premedication [7,12], as it prevents mild symptoms that could interfere with the procedure and increase patient anxiety. Moreover, the first desensitization should be applied in the intensive care unit, not only for safety reasons, but also to reassure patients about the procedure. In our experience, diminishing patient stress makes subsequent desensitization easier.

We should bear in mind that the patient is constantly monitored. We think that while premedication does not completely protect against a severe allergic reaction, it is useful. Failed attempts to administer a drug that caused a hypersensitivity reaction using only premedication have been published [13]. Zorzou et al [14] used premedication and slow delivery; however, 77% of patients had a mild reaction, and the remaining patients could not achieve the total dose [14].

In conclusion, desensitization with chemotherapy agents could resolve an important problem for patients with cancer. However, this procedure involves a certain degree of risk. Our results show that it can be performed much more quickly than reported by other authors. Further studies are needed to compare outcomes from different protocols in order to be able to define indications for different approaches.

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