



Rapid desensitization to chemotherapy drugs in oncologic patients. A good and safe option. A two-case presentation

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RESUMEN

Las reacciones de hipersensibilidad, anafilácticas o anafilactoides a los quimioterápicos oncológicos, como platinos, taxanes, anticuerpos monoclonales y otros, limitan su utilidad terapéutica por el temor de los médicos tratantes a inducir reacciones graves o fatales en los pacientes que han presentado reacciones previas con los mismos. Esto lleva a que se utilicen otros esquemas de quimioterapia menos efectivos o de segunda elección para la sensibilidad del tumor. La desensibilización rápida a este tipo de medicamentos en pacientes que han tenido reacciones previas es un procedimiento seguro y de efectividad comprobada, que permite administrar a los pacientes oncológicos los quimioterápicos más adecuados para la sensibilidad tumoral, aunque hayan mostrado anteriormente reacciones de hipersensibilidad a los mismos. A pesar de la eficacia y tolerabilidad demostrada en los protocolos de desensibilización rápida a quimioterápicos en múltiples trabajos previos, sigue siendo un procedimiento subutilizado, tal vez por desconocimiento o temor a desencadenar una reacción grave en los pacientes. Se comunican dos casos exitosos de desensibilización rápida, uno con trastuzumab (Herceptin), un anticuerpo monoclonal y otro con docetaxel (Taxotere) un taxane semisintético, ambos productos utilizados para el tratamiento de cáncer de mama. La finalidad de esta presentación es difundir entre los oncólogos, alergólogos, enfermeras que aplican quimioterapias y en general a todo el personal médico relacionado con pacientes oncológicos, las bondades de estos protocolos de desensibilización rápida a quimioterápicos en pacientes con reacciones previas de hipersensibilidad. La relativa facilidad para llevarlos a cabo y el alto porcentaje de éxito que se consigue nos impulsan a promover un uso más frecuente y universal de estos procedimientos.

Palabras clave: quimioterapia, hipersensibilidad, desensibilización rápida.

ABSTRACT

Hypersensitivity reactions, and anaphylactic or anaphylactoid reactions to oncologic chemotherapy drugs, such as platinum, taxanes, monoclonal antibodies and others, limit their therapeutic use due to the fear of the treating physician to induce severe or deadly reactions in patients who have presented previous reactions to the same. This leads to the use of less effective or second line chemotherapy schemes for the sensitivity of the tumor. The rapid desensitization to such medications in patients who have presented previous reactions is a safe and proven effective procedure, which allows the use of the most effective chemotherapy drugs for the tumor sensitivity in oncologic patients even if they have presented hypersensitivity reactions to those drugs previously. In spite of the effectiveness, safety and tolerance demonstrated in fast desensitization to chemotherapy drug protocols in previous works, it remains an underutilized procedure, perhaps due to ignorance and/or fear of triggering a serious reaction in patients. Two successful cases of fast desensitization are hereby presented, one with trastuzumab (Herceptin), a monoclonal antibody, and another with docetaxel (Taxotere), a semisynthetic taxane, both products utilized for the treatment of breast cancer. The purpose of this presentation is to disseminate among oncologists, allergists, nurses applying chemotherapy and in general to all medical personnel related to cancer patients, the benefits of such rapid desensitization to chemotherapy drug protocols in patients with previous hypersensitivity reactions. The relative ease to accomplish them and the high percentage of success that is achieved encourage us to promote more frequent and universal use of these procedures.

Key words: chemotherapy, hypersensitivity, desensitization, immunologic.

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Adverse drug reactions have been defined as drug-induced alterations. They produce an estimated 3% to 9% of hospital admissions, have been reported in as many as 81% of hospitalized patients, occur in 25% of outpatients, and represent the 4th to 6th leading cause of death in hospitalized patients.¹⁻³ Reactions to drugs can be classified into predictable and unpredictable. Predictable reactions are the result of the pharmacological action of the drug. Unpredictable reactions may be due to idiosyncrasy,

intolerance or may have an immunological basis, such as IgE mediated reactions. IgE-mediated reactions are called allergic or anaphylactic and reactions in which IgE is not involved are called anaphylactoid or pseudoallergic as those occurring with vancomycin (red man syndrome), contrast media or taxanes.¹⁻³

Chemotherapy drugs such as taxanes, platinum, doxorubicin, monoclonal antibodies and others can cause hypersensitivity reactions both anaphylactic and anaphylactoid. These reactions are common and the mechanisms responsible for them are not well elucidated and vary between different drugs. The symptoms in these reactions range from mild skin rashes to more severe reactions such as arthralgia, cardiorespiratory alterations and death. The objective in cancer patients who present hypersensitivity reactions to chemotherapy is to treat them by rapid desensitization, looking to continue and complete the antineoplastic regimen.⁴ In order to provide cancer patients with hypersensitivity reactions to drugs the best chemotherapy schemes, Castells et al, from Brigham and Women's Hospital in Boston, have developed some successful rapid desensitization schemes, which have been used 413 times in a group of 98 patients with different chemotherapy agents, achieving that 100% of patients completed the full doses of chemotherapy.⁵⁻⁷

The rapid desensitization to a drug was initially carried out with penicillin 50 years ago. Desensitization is an empirical procedure, which induces temporary clinical tolerance to a drug, by administering gradually increasing small doses to complete the total therapeutic dose in patients who had previously developed hypersensitivity reactions to the drug. More recently, rapid desensitization protocols to chemotherapy drugs such as taxanes, platinum, doxorubicin, monoclonal antibodies and others have been developed.^{6,8,9} The term "rapid desensitization" indicates that a total therapeutic dose can be achieved in a relatively short time, typically from 4 to 12 hours.

The aim of rapid desensitization is to induce temporary clinical tolerance with few or no side effects while increasing the dose of the drug to reach therapeutic range. The initial dose is gradually increased at fixed intervals of time or as continuous infusion up to total dose. The initial dose may be 10 to 10,000 times less

than the therapeutic dose and the increases are made every 10 to 30 minutes by doubling or tripling the dose in each new application.

Two cases of patients with breast cancer who underwent rapid desensitization are presented; one of the cases to trastuzumab (Herceptin) and the other one, a patient that presented a hypersensitivity reaction to docetaxel (Taxotere). To carry out desensitization, the standardized protocol of Castells, from Brigham and Women's Hospital in Boston, which includes three solutions and 12-steps of infusion allowing the patient to receive a full therapeutic dose over a period of time of 5 to 8 hours, was used (Table 1). This protocol is the one Castells and associates have used in 413 successful desensitizations in patients with hypersensitivity reactions to carboplatin, cisplatin, paclitaxel, doxorubicin, rituxumab, transtuzumab, infliximab and others in the course of several years.^{3,5,6}

PATIENT 1

Female patient, 53 years old, with no previous medical history including allergies, to whom on May 24, 2005 an inflammatory breast cancer was diagnosed (poorly differentiated breast adenocarcinoma high nuclear grade). On May 31, Taxol 80 mg and Herceptin 4 mg/kg per week were started. Two days after the first dose was applied, the patient developed skin disease with generalized maculopapular rash, burning and itching skin. The patient presented purple skin lesions in the lower limbs a day after. This reaction was treated with oral deflazacort (corticosteroid), 30 mg every 24 hours for 10 days and oral ceterizine, 10 mg every 12 hours for 5 days and then 10 mg at night for 10 days. The patient improved rapidly, chemotherapy was suspended and she was treated with radiation.

On February 15, 2006 it was decided to retry herceptin treatment for which a preventive scheme of oral corticosteroids and H-1 antihistamines 3 days before the application of chemotherapy was prescribed, but again, the same skin reaction in the first application appeared. As a result of this second reaction, it was decided to use Taxol only in her treatment which was well tolerated. In October 2006, due to the clinical evolution and tumor

characteristics, the oncologist decided that Herceptin was the treatment of choice, therefore an evaluation by allergology was requested and it was decided together to conduct rapid desensitization. On October 17, 2006 the patient was interned in the intensive care unit, pre-treated with corticosteroids and oral antihistamines H-1, monitored, with a permeable vein and the presence of intensive care physicians. Rapid desensitization was begun under the protocol recommended by Castells. The patient tolerated the entire procedure without any reactions and the first therapeutic dose of trastuzumab (Herceptin) was attained in a period of 5 hours. The patient was dismissed 3 hours after completion of the procedure and then she continued with her applications of trastuzumab (Herceptin) in an outpatient chemotherapy department to complete an overall scheme in May 2007 without presenting new hypersensitivity reactions.

PATIENT 2

Female patient, 42 years old, with evident atopic history and a history of allergic rhinitis and who was referred for

the first time to our service by the oncologist on September 22, 2006. The patient had a diagnosis of infiltrating ductal adenocarcinoma with bone metastases and the reason for her referral was a hypersensitivity reaction during the second dose of docetaxel (Taxotere) 75 mg/m². The patient developed dermatosis with cutaneous erythema and purpuric lesions in the lower limbs as well as an attack on mucous membranes. This reaction was treated with oral corticosteroids (prednisone) and H-1 antihistamines (hydroxyzine), yielding completely. A change of treatment or rapid desensitization was suggested to the oncologist, and the second choice was decided, which took place on September 28, 2006. The patient was admitted to the intensive care unit, pre-treated with H-1 antihistamines and corticosteroids, monitored, with a permeable vein and the presence of intensive care physicians, and the same protocol of 3 solutions and 12 steps was utilized, achieving, in a period of 5 hours, a total dose of 75 mg/m² of docetaxel, without any reaction or discomfort. After that, docetaxel continued being applied by the outpatient chemotherapy department until the complete scheme was finished without presenting any new reactions.

Table 1. Standard desensitization protocol using a total dose of 500 mg as an example

<i>Total dose</i>	<i>500 mg</i>	<i>Solution concentration</i>	<i>Total dose in each solution (mg)</i>		
Solution A	250 mL	0.02 mg/mL	5.0		
Solution B	250 mL	0.20 mg/mL	50.0		
Solution C	250 mL	2.00 mg/mL	500.0		
<i>Step</i>	<i>Solution</i>	<i>Rate (mL/h)</i>	<i>Time (min)</i>	<i>Administered dose (mg)</i>	<i>Cumulative dose infused (mg)</i>
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500.000
			Total time: 5.82 h	Total dose infused: 500 mg	

DISCUSSION

In the treatment of cancer, more chemotherapeutic agents of different types are increasingly being used, which has made hypersensitivity reactions to these drugs more common.¹⁰ These unexpected reactions, outside the known toxicity of the drug, are associated with certain categories of antineoplastic agents such as taxanes, platinum-containing compounds, epipodophyllotoxins, monoclonal antibodies and others. The mechanisms responsible for these hypersensitivity reactions are not well elucidated and vary among different drugs. For example, during the infusion of CD20 antibodies in patients with leukemia and it is associated with the release of cytokines TNF, IL-6 and IL-8 in high concentrations.¹ Other mechanisms that have been involved are activation of complement by lipophilic excipients; possible tumor lysis and other complex biological effects such as cytokine release.⁷

The monoclonal antibodies, cetuximab, rituximab, trastuzumab, etc., are new antineoplastic agents that target specific receptors on malignant cells. They have a high incidence of hypersensitivity reactions, 40% for trastuzumab, 77% for rituximab and 19% for cetuximab. The clinical manifestations of hypersensitivity occur during the first or second drug application and vary from mild reactions as a rash to severe reactions as bronchospasm, chest pain and anaphylaxis. The pathogenesis of hypersensitivity reactions by monoclonal antibodies is unclear, but since they often happen during the first application, it is demonstrated that prior sensitization is unnecessary and that the reactions are probably induced by the release of cytokines.⁴

Hypersensitivity reactions are common with taxanes. With paclitaxel, they happen in just over 30% of patients and most of the reactions occur in the first or second dose; therefore, it is very likely that they are not IgE-mediated. Although docetaxel is a semisynthetic taxane it has been shown that it can have a cross-reactivity with paclitaxel 90%.¹⁰

In the cases presented in this report, in one of them, trastuzumab (Herceptin), a monoclonal antibody derived from human recombinant DNA which is designed to attack tumor cells selectively, acting at the site of extracellular action of the receptor 2 of the human epi-

dermal growth factor (HER 2+) was used. This antibody is a IgG1 containing human regions that complement determining regions of an antibody anti-p185HER2 murine that binds to the HER2 receptor. In the second case, a taxane (docetaxel) a semisynthetic chemotherapy agent obtained from a European tree (*Taxus baccata*) was used. Both patients had cutaneous hypersensitivity reactions since the first application which reflects non-IgE-mediated reactions or anaphylactoid.

Hypersensitivity reactions have limited the use of antineoplastic drugs for fear of inducing severe reactions or death.¹¹

The need to provide first-line treatments in primary or recurrent cancers has been the stimulus for the clinical development of rapid desensitization techniques to chemotherapy agents and monoclonal antibodies in patients who have had hypersensitivity reactions including anaphylaxis.^{5,6,11} The development of rapid desensitization treatment of hypersensitivity to drugs is designed to use essential drugs while protecting patients from severe reactions induced by anaphylactic or anaphylactoid mechanisms.^{3,12} In one of our two cases, a different treatment was attempted after the first reaction, but did not work. For this reason, and knowing the excellent results in patients reported by Castells it was decided to attempt desensitization to trastuzumab (Herceptin) and docetaxel (Taxotere) with the recommended protocol in their work.^{3,5,6,11}

In the rapid desensitization to a drug there is a temporary induction of immunological tolerance to its antigens, which allows the patient to tolerate medications that have produced a prior hypersensitivity reaction. What you do is to gradually introduce small amounts of the drug until a full therapeutic dose is reached. In order to achieve this, different protocols have been developed.^{5,6}

In rapid desensitization, a total therapeutic dose can be achieved in a period of 4 to 12 hours. In our patients we managed to reach the therapeutic dose in a period of approximately 5 hours without a hitch and patients continued to receive, as outpatients, doses of trastuzumab (Herceptin) and docetaxel (Taxotere) until completing the scheme. Although these procedures are becoming more frequent, the cellular and molecular mechanisms of desensitization

are not fully elucidated.^{5,12} It seems that in these fast desensitization procedures mast cells and basophils are involved as target cells, as well as Syk which is a signal transduction molecule and whose deficiency prevents basophils to respond to antigens of medicines and STAT6, a signal transducer responsible for activating the transcription for IL-4 and IL-13.^{4,5}

All rapid desensitization protocols currently available are empirical and based on previous protocols of desensitization to antibiotics by trial/error clinical experience.^{3,12}

The temporary clinical tolerance that is achieved in hours with desensitization can be maintained if the antigens of the drugs are given at regular intervals depending on the pharmacokinetic parameters.

The recommendation for a rapid desensitization must be made by a specialist in allergy and immunology and must be carried out in an intensive care unit, with nursing and staff trained in resuscitation.^{4,5,7}

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