Original Article

Outcome of 490 Desensitizations to Chemotherapy Drugs with a Rapid One-Solution Protocol

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What is already known about this topic? Rapid desensitization protocols are effective and safe and allow reintroduction of a drug in patients who are sensitized to it.

What does this article add to our knowledge? It shows our center experience with a new, shorter protocol using only 1 solution of the drug.

How does this study impact current management guidelines? It could contribute to abbreviated desensitization protocols, at least in selected patients, reducing cost and time and allowing desensitization to be available for more patients.

BACKGROUND: Hypersensitivity reactions to chemotherapy drugs are quite frequent. Desensitization for chemotherapy drugs has become an option to maintain first-line therapy in patients who have suffered such reactions.
OBJECTIVE: The objective of this study was to describe our experience in desensitization with antineoplastic agents using a rapid 1-solution protocol.
METHODS: We performed a 3-year prospective observational study recording all patients who were desensitized with this protocol. All patients signed an informed consent. Skin test was performed at concentrations previously described as nonirritant. Desensitization was performed using only 1 solution of the drug prepared following the manufacturer instructions. Most drugs were diluted in a volume of 500 mL. We started infusion at 5 mL/h and increased doses at 15-minute intervals to 10, 25, 50, 75, and 100 mL/h. If no reaction occurred, and if the pharmacokinetics of the drug allowed it, we stepped up to 150, 200, and 250 mL/h.
RESULTS: Ninety patients were desensitized to 93 drugs: oxaliplatin (30), carboplatin (16), paclitaxel (19), docetaxel (6), cetuximab (5), rituximab (6), and others (11). A total number of 490 procedures were performed. Sixteen patients (17.77%) presented 26 reactions (5.3%). Most reactions appeared in patients who were desensitized to platins and in patients with severe reactions. All but 3 cycles were completely administrated. No deaths or hospital admissions were recorded.
CONCLUSIONS: This 1-solution protocol for desensitization has demonstrated to be safe and useful in our study population, especially for mild-to-moderate reactions and nonplatinum drugs. If our results were reproducible in other centers and larger populations, they could contribute to simplifying protocols and making desensitization available for more patients. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Rapid drug desensitization; One-solution protocol; Drug allergy; Oxaliplatin; Carboplatin; Paclitaxel; Docetaxel; Cetuximab; Rituximab*

Desensitization has proved to be safe and effective in management of hypersensitivity reactions to chemotherapy drugs. Different protocols have been described, most of them involving the use of 3 or more solutions of the drug.[1-3] Currently, the most popular approach is the rapid protocol of 3 solutions and 12 steps published before by Castells et al,[2] although faster 1- or 2-solution protocols have been recently described.[4-6]

The aim of this study was to present a prospective observational study showing our experience in desensitization with antineoplastic agents and monoclonal antibodies using a protocol with 1 solution of the drug.

MATERIAL AND METHODS

We recorded demographic and clinical data of patients who were desensitized to chemotherapy drugs or monoclonal antibodies for cancer therapy between January 2013 and December 2016. All patients were informed, and they signed an informed consent.

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Abbreviations used
CTCAE v.3- Common Terminology Criteria for Adverse Events, Version 3.0
IDT- Intradermal test
SPT- Skin prick test
ST- Skin test

Severity of initial reaction was classified in 3 grades according to Brown's classification[7] (Table I).

This study has been approved by our Institution's Ethical Committee (CI.PI-15/14).

Skin testing

Skin test (ST) was performed 1 or 2 weeks after the initial reaction in most patients.

Skin prick test (SPT) was performed on the volar surface of the forearm. Concentrations were 5 mg/mL for oxaliplatin, 1 mg/mL for cisplatin, 10 mg/mL for carboplatin, 6 mg/mL for paclitaxel, 1 mg/mL for docetaxel, 0.12 mg/mL for irinotecan, 2 mg/mL for cetuximab, 10 mg/mL for rituximab, and 10 mg/mL for leucovorin. Intradermal testing (IDT) was performed first at 1/1000 and, if negative, at 1/100 and 1/10 dilution of the concentration used for SPT.

Patients with immediate reaction to cetuximab underwent SPT with commercial extracts of cow and pork meat (Leti SA, Barcelona, Spain) to exclude sensitization to alfa-gal.[8]

Desensitization procedure

The decision to perform desensitization was made together with an oncologist and only on the basis of clinical indication. It was offered if the oncologist thought that a clinical benefit could be obtained from continuing the drug and the patient presented at least 1 reaction to a chemotherapy agent with type I hypersensitivity and/or moderate or severe infusion reaction compatible symptoms despite negative ST results.

Desensitization was not performed when symptoms were compatible with immune-mediated delayed reactions (hypersensitivity syndrome, Stevens-Johnson syndrome, serum sickness, or toxic epidermal necrolysis), when patient did not give his/her consent, or the oncologist did not advise continuation of the inciting drug.

Most procedures were performed in an outpatient setting, in the allergy unit or in the outpatient oncology unit. Hospitalization and/or stay in the intensive care anesthesiology unit were considered for patients with very severe reactions, previous concomitant diseases, and/or long chemotherapy protocols. All procedures were directly supervised by an allergist trained in desensitization.

All patients received dexchlorpheniramine 5 mg and ranitidine 50 mg intravenous 30 minutes before desensitization. Aspirin (200-500 mg every 24 hours since day before), montelukast (10 mg every 24 hours since day before), and cetirizine (10 mg every 12 hours since 3 days before) were given according to clinical symptoms and severity of the reaction.

Montelukast was given to all patients who had respiratory symptoms and to those patients with the previous history of asthma or chronic obstructive respiratory disease despite the type of reaction. Aspirin was given to all patients who did not have contraindication for it. We avoided it if there was recent surgery (in the 2 weeks before desensitization), thrombocytopenia, nonsteroidal anti-inflammatory drug hypersensitivity, active bleeding, or gastric ulcer. Most patients received 200 mg, some subjects with very severe reaction or who reacted in a previous desensitization received 500 mg at the allergist discretion. Oral antihistamines were added in patients with severe reaction and/or highly positive ST, in patients who reacted in a previous desensitization, and in patients with previous chronic urticaria.

TABLE I. Brown's classification for grading generalized hypersensitivity reactions[7]

Grade	Symptoms
I Mild: skin symptoms	Generalized erythema, urticaria, periorbital edema, or angioedema
II Moderate: cardiovascular, respiratory, or gastrointestinal involvement	Dyspnea, stridor, wheeze, nausea, vomiting, presyncope, diaphoresis, chest or throat tightness, or abdominal pain
III Severe: hypoxia, hypotension, or neurologic compromise	Cyanosis or hypoxia ($SpO_2 < 92\%$), hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence

SpO_2, Peripheral capillary oxygen saturation.

We also used corticosteroid (methyl prednisolone 1 mg/kg of weight or hydrocortisone 100 mg) in the first 15 patients and in patients desensitized to rituximab. Dexamethasone 20 mg was given orally 12 hours and 1 hour before the treatment to patients receiving paclitaxel, docetaxel, and pemetrexed.

In addition, premedication for antiemesis was prescribed by the oncologist according to the current guidelines.[9] Drugs used included, not exclusively, metoclopramide, ondansetron, aprepitant, and palonosetron.

The desensitization protocol was performed, as we described previously,[6] using 1 solution of the drug prepared following manufacturer instructions.

Briefly, the dose of each agent was calculated by the oncologist on the basis of the body surface area and clinical parameters. Drugs were prepared in sterile conditions by the Pharmacy Service to obtain a full-strength nondiluted solution that was used for desensitization. The total volume of the solution was 500 mL for platines, taxanes, and rituximab, 250 mL for cetuximab and calcium folinate, and 100 mL for pemetrexed. Concentration varied among patients and drugs, as it was the same concentration for a patient receiving the same dose in a standard infusion.

Infusion of the drug was initiated at 5 mL/h and increments were done each 15 minutes to 10, 25, 50, 75, and 100 mL/h. If no reaction appeared, and depending on the drug, 150, 200, and 250 mL/h were reached at 15-minute intervals.

When a reaction appeared, we stopped infusion and gave treatment if indicated. When symptoms resolved, we restarted the protocol in the last well-tolerated step.

Maximum rate of infusion never went beyond the recommended rate by the oncologist for each drug. Briefly, maximum infusion rates prescribed for any patient in our hospital are 250 mL/h for oxaliplatin, 500 mL/h for carbopatin, 250 mL/h for cisplatin, 175 mL/h for paclitaxel, 250 mL/h for docetaxel, 250 mL/h for calcium folinate, 250 mL/h for rituximab, and 250 mL/h for cetuximab. Table II shows an example of dosage for oxaliplatin.

RESULTS

Ninety patients (60 females, median age 57.34, standard deviation 10.02) underwent at least 1 desensitization procedure to