LETTER TO THE EDITOR

Outcomes with one-bag desensitization protocol for biologic and chemotherapy agents in 451 procedures

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To the Editor:

Rapid drug desensitisation is an essential procedure to allow the maintenance of first-line treatments in patients suffering from hypersensitivity reactions (HSR) to biological and chemotherapeutic agents (1-6).

Since our first description of the one-bag drug desensitisation protocol in 2016 (2), several groups have implemented it in their clinical practice (1-8), demonstrating its good tolerance and efficacy.

In addition to the already proven effectiveness and security of the one- bag protocol, throughout these years of clinical practice we have been able to reduce the time of the standard procedure with no further appearance of adverse events, by shortening its initial steps, making it a more convenient option for both physicians and patients.

In this setting, we present the results of the application of the one- bag desensitization in two different hospitals of our region (Complejo Hospitalario Universitario de Santiago de Compostela and Ferrol), along six years of experience.

From April 2016 to December 2022, a total of 451 rapid desensitisation procedures were performed in 86 patients (77% women, mean age 68 years-old [range, 19-85]). More than one third of the patients (36%) had been diagnosed with ovarian cancer. The remaining patients suffered from breast (18%), colon (9%), prostate (7%), endometrium (7%), lung (4,5%), lymphoma (4,5%), uterus (3%), gastric (3%), liver (2%), gallbladder (1%), rectum (1%), kidney (1%) and central nervous system cancers (1%). Platinum salts were the most common drugs involved in HSR (45%), shortly followed by taxanes (34%), biological therapies (18%), and alkylating agents (1%).

Most of the reactions had occurred during the first minutes after the administration of the drug involved in the reaction and had been well documented by the oncologist in charge who shortly after asked for allergic evaluation. Regarding the severity, 56% of the reactions were moderate while 20% were mild and 24% were severe, according to Brown's classification (10).

Between 15 and 21 days after the reaction, and prior to desensitisation, patients underwent allergological assessment and according to the suspected immunological mechanism involved,

skin testing were performed, if needed. For this purpose, standardised concentrations and doses approved for each agent were used (3).

Only 42% of the patients did react against skin tests (92% of them with immediate positivity), being platinum salts the most frequently drugs responsible for these results. Thus, 87% of the patients with platinum salt hypersensitivity showed a positive result. However, 97% of taxanes and 100% of biologics were tested negative, which is consistent with other previously published series (8). Two patients with a suspected non IgE-mediated reaction to rituximab and temozolamide were not skin tested.

Desensitisations were performed in a short-stay hospital bed under the supervision of a chemotherapy nurse and an allergist. Informed consent was obtained prior to the desensitization procedure. Patients received standard oncologic premedication for their drug and premedication according to the symptoms and type of their initial HSR as previously suggested (8). Dexchlorpheniramine 5 mg IV was administered to every patient 5 minutes before starting the procedure (3).

According to our previously published protocol, once the dose required for each patient had been calculated, it was diluted in 0.9% saline solution for taxanes and biological agents and in 5% dextrose solution for platinum salts to reach a final concentration of 1 mg/mL, 0.5 mg/mL or 0.1 mg/mL, depending on the total amount of the drug so that the volume to be administered differed from patient to patient (an example of the protocol, with a total amount of 650 mg of drug to be administered and a required concentration of 1 mg/ml can be found in Table 1). The line (15 Micron Filter in Sight Chamber, polyethylene-lined light-resistant tubing, distal microbore tubing 272 cm/12 mL) was primed with the antineoplastic agent and clamped. The distal line was connected to a 3-way stopcock (BD Connecta, Becton Dickinson Infusion Therapy, Stockholm, Sweden). An infusion pump with automated multistep infusion options (Icumedical Plum360, ICU Medical BV, The Netherlands) was used, but infusion rates were changed manually every 15 minutes until the last two steps when infusion rates were changed after 30 minutes.

Using this standard protocol, the duration of the procedure was 4:30 hours for every patient. However, most recently, we have implemented in our daily clinical practice a shortened schedule in those patients who had well tolerated the first desensitization cycle. Thus, in a total of 17 patients and 93 desensitizations, the procedure was shortened, removing a mean of the 4 initial steps from the protocol, and consequently, reducing the time of the procedure to a mean of 3:30 hours.

Using the one-bag procedure, all the patients were able to receive the complete dose of their drug. However, despite desensitization, 7 patients (57,4% of them with a severe initial HSR), experimented a HSR during the drug administration. In 43% of them, the HSR appeared in the first desensitization cycle and 43% continued experiencing HSR in two or more cycles. The percentage of patients suffering from HSR using our procedure (8,1%) was fewer than in other multiple-bag and one-bag desensitization protocols (1,11). Most of the reactions were moderate (57,4%) and were successfully treated. None of the patients who underwent the shortened protocol experienced any adverse events. The clinical characteristics of these patients, including the number of previous tolerated cycles, description of the reaction and results of skin tests with the drug involved in the reaction, are shown in Table 2.

In conclusion, we present an extension of our previously published protocol (2), increasing the number of patients in our series, proving its safety and well- tolerability. We also propose a quickest version of the protocol, shortening its initial steps with no further appearance of

hypersensitivity reactions. Thus, we consider the one- bag procedure to be the best and more convenient option for both clinicians and patients for the management of HSR in either low, moderate or high-risk patients in daily clinical practice.

Conflicts of interest:

IRV: declare no conflict of interest regarding this manuscript

PMB: declare no conflict of interest regarding this manuscript.

MCM: declare no conflict of interest regarding this manuscript.

MGR: declare no conflict of interest regarding this manuscript.

PIS: declare no conflict of interest regarding this manuscript.

RLA: declare no conflict of interest regarding this manuscript.

SCM : declare no conflict of interest regarding this manuscript.

TGF: declare no conflict of interest regarding this manuscript.

SLF: Expert Witness (Serving as an expert witness, consultant or otherwise providing a deposition, testimony,or other information, analysis or document for a lawsuit, government agency proceeding, grand jury, or other legal proceeding, even if the case did not go to trial): ALK, ALLERGY THERAPEUTICS

MAG: declare no conflict of interest regarding this manuscript.

VRV: declare no conflict of interest regarding this manuscript.

CVP: declare no conflict of interest regarding this manuscript.

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Desensitization schedule for 1 mg/mL concentration

	Dose:	650	*mg*
Step	**Time (min)**	**Rate (mL/h)**	**Dose (mg)**
1	15	0,2	0,05
2	15	0,3	0,075
3	15	0,7	0,175
4	15	1,3	0,325
5	15	1,6	0,4
6	15	3,25	0,8125
7	15	6,5	1,625
8	15	13	3,25
9	15	16	4
10	15	33	8,25
11	15	65	16,25
12	15	130	32,5
13	15	144	36
14	15	289	72,25
15	30	361	180,5
16	30	578	Remaining 293,5375

Table 2. Clinical characteristics of patients with HSR during desensitization						
Age (Gender)	Cancer	Drug	HSR`s cycle (Severity) [Latency]	Skin test result	Number of procedures	Number of HSR during desensitization (description)
36 (F)	Cervix	Paclitaxel	1st (moderate) [immediate]	Negative	3	1 1st cycle, step 1: five minutes after starting the infusion, two self-limited hives which resolved with no treatment.
44 (F)	Ovary	Paclitaxel	1st (moderate) [immediate]	Negative	3	3 1st cycle, step 14: warmth sensation in the scalp, face, chest erythema, and palmar itching. Cycle was completed without requiring further medication. 2nd cycle, last step: retroauricular itching with mild erythema. Treated with dexchlorpheniramine with recovery in 15 minutes. 3rd cycle, step 15: face, ear and chest warmth with erythema. Treated with hydrocortisone, being able to continue the procedure after 10 minutes with no further complications.
78 (F)	Linfoma	Rituximab	1st (moderate) [immediate]	Negative	4	1 1st cycle step 15: chills and hypotension. Paracetamol and methylprednisolone were administered after stopping the procedure. Desensitization completed afterwards.
70 (M)	Lung	Oxaliplatin	10th (severe) [immediate]	Negative	4	2 3rd cycle, step 15: shivering followed by dizziness and sweating, dyspnea, desaturation and chest oppression at step 16. 4th cycle, step 13: face erythema treated with dexchlorpheniramine. At step 15, chills, tachycardia and desaturation treated with salbutamol, IV corticosteroids and ipratropium bromide, being able to continue with the procedure.
68 (F)	Breast	Trastuzumab	1st (severe) [immediate]	Negative	12	1 5th cycle, step 15: facial erythema, dyspnea and headache treated with antihistamines and corticosteroids, completing the cycle.
52 (F)	Ovary	Carboplatin	2nd (moderate) [immediate]	Positive	10	1 10th cycle, step 16: eyelid, mandibular, neck, chest and palms of hands erythema and itching.
69 (F)	Ovary	Carboplatin	2nd (severe) [immediate]	Positive	7	3 1st cycle, step 9: erythema in forearms treated with antihistamines and corticosteroids. 2nd cycle, step 12 generalized erythema, requiring adrenaline. Cycle was completed afterwards. 3rd cycle, step 14: generalized erythema treated with antihistamines and corticosteroids.