

Journal Pre-proof

One-dilution rapid desensitization protocol to chemotherapeutic and biological agents: a five-year experience

Anna Sala-Cunill, MD PhD, Gustavo-Jorge Molina-Molina, MD, Jenny-Tatiana Verdesoto, MD, Moisés Labrador-Horrillo, MD PhD, Olga Luengo, MD PhD, Paula Galvan-Blasco, MD, Mar Guilarte, MD PhD, Victoria Cardona, MD PhD

PII: S2213-2198(21)00712-1

DOI: <https://doi.org/10.1016/j.jaip.2021.06.024>

Reference: JAIP 3690

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 16 January 2021

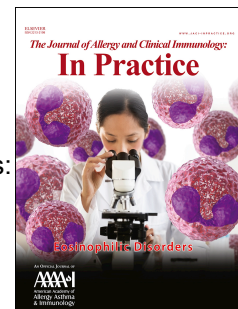
Revised Date: 10 June 2021

Accepted Date: 11 June 2021

Please cite this article as: Sala-Cunill A, Molina-Molina GJ, Verdesoto JT, Labrador-Horrillo M, Luengo O, Galvan-Blasco P, Guilarte M, Cardona V, One-dilution rapid desensitization protocol to chemotherapeutic and biological agents: a five-year experience, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.06.024>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology



TITLE:

One-dilution rapid desensitization protocol to chemotherapeutic and biological agents: a five-year experience

Authors:

Anna Sala-Cunill MD PhD^{1,2,3,4*}, Gustavo-Jorge Molina-Molina MD^{1,3*}, Jenny-Tatiana Verdesoto MD¹, Moisés Labrador-Horrillo MD PhD^{1,2,3,4}, Olga Luengo MD PhD^{1,2,3,4}, Paula Galvan-Blasco MD^{1,3}, Mar Guilarte MD PhD^{1,2,3,4\$}, Victoria Cardona MD PhD^{1,2,3,4\$}

* These two authors contributed equally to this work.

\$ These two authors contributed equally to this work and share senior authorship.

Author's institutional affiliations:

¹Allergy Section. Internal Medicine Department. Hospital Universitari Vall d'Hebron, Barcelona, Spain

²ARADyAL research network. Instituto de Salud Carlos III (ISCIII). Spain

³Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain.

⁴Universitat Autònoma de Barcelona (UAB). Barcelona. Spain

E-mail from the authors:

Anna Sala-Cunill MD PhD: asala@vhebron.net

Gustavo-Jorge Molina-Molina MD: gumomo13@hotmail.com

Jenny Tatiana Verdesoto: jennyta.230891@gmail.com

Olga Luengo MD PhD: oluengo@vhebron.net

Paula Galván Blasco: pgalvan@vhebron.net

26 Mar Guilarte MD PhD: mguilarte@vhebron.net

27 Moisés Labrador-Horrillo MD PhD: mlabrador@vhebron.net

28 Victoria Cardona MD PhD: vcardona@vhebron.net

29

30 **Corresponding author:**

31 Moisés Labrador-Horrillo MD PhD

32 Email: mlabrador@vhebron.net. Phone: +34 93 2746169

33 ORCID: 0000-0003-3222-2380

34 Hospital Universitari Vall d'Hebron

35 Allergy section Internal Medicine Department

36 Passeig Vall d'Hebron 119-129. 08035. Barcelona

37

38 **Statement of contribution of authors:**

39 ASC, GJMM, MLH, MG and VC contributed to study conception, design and drafting
40 of the manuscript and had full access to all the data in the study and takes responsibility
41 for the integrity of the data and the accuracy of the data analysis.

42 All the authors have participated in the clinical data collection, data analysis and
43 interpretation and, they have read and approved the final version of the manuscript.

44

45 No conflict of interest for all authors

46

47 Text word count: 3294.

48 Abstract's word count: 248.

49 Abstract

50 BACKGROUND:

51 Rapid drug desensitization (RDD) becomes a crucial procedure to allow treatment
52 continuation in patients who suffer drug hypersensitivity reactions (DHRs) to
53 chemotherapeutic (CMT) and biological agents (BA).

54 **OBJECTIVE:** The aim of the study was to compare the efficacy and safety of a one-
55 bag-dilution-protocol (1DP) with a conventional three-bag-dilution-protocol (3DP) for
56 desensitization of patients with CMT or BA hypersensitivity.

57 METHODS:

58 Retrospective analysis of patients with immediate DHRs to CMT or BA who underwent
59 at least one RDD procedure in our department between 2014-2019. Demographical data,
60 clinical history, skin tests, tryptase levels and risk assessment were registered. The
61 safety, tolerability, occurrence and severity of breakthrough reactions (BTR) with 3DP
62 and 1DP were compared.

63 RESULTS:

64 After the allergy workup, 157 patients fulfilled criteria to undergo RDD (137 females,
65 mean age 60.44 ± 12.6 years). 639 RDDs (543 CMT and 96 BA) were performed using
66 3DP in 205 (48 patients) and 1DP in 434 (109 patients). Almost all procedures (636)
67 were completed successfully.

68 No BTR occurred in the first RDD in 52% and 51% of the 3DP and 1DP respectively.
69 Most BTR were mild. Moderate-severe BTR occurred in 17% with 3DP and 9% with
70 1DP. There were no statistical differences between protocols regarding the rate and
71 severity of BTR.

72 CONCLUSIONS:

73 Rapid drug desensitization with 1DP to CMT and BA has equivalent outcomes in terms
74 of efficacy, tolerability and safety when compared with a 3DP desensitization in a
75 selected population of patients. Moreover, 1DP reduces the time required for RDD and
76 simplifies the logistics.

Keywords: Rapid Drug Desensitization, Drug allergy, One-bag solution protocol, Chemotherapeutic and biological agents

Highlights box:

What is already known about this topic?

Rapid desensitization applying multi-bag protocols with serial dilutions are widely used in patients with hypersensitivity reactions to biologics and chemotherapeutic agents. Such procedures are time consuming, impacting patients and healthcare resources.

What does this article add to our knowledge?

This article shows that the one-bag desensitization protocol (non-diluted), with chemotherapeutic and biological agents, is non-inferior regarding efficacy and safety compared to the conventional three-dilution protocol.

How does this study impact current management guidelines?

Implementing one-bag desensitization protocols may allow simplifying preparation in the pharmacy, reducing the workload for nurses (no bag change, fewer steps), decreasing the risk of errors and shortening the duration of the procedure, without hampering efficacy or safety.

Abbreviations:

- Rapid Drug Desensitization (RDD)
- Drug Hypersensitivity Reaction (DHR)
- Chemotherapeutic (CMT)
- Biological agent (BA)
- One-bag dilution protocol (1DP)
- Three-bag dilution protocol (3DP)

- 102 • Breakthrough reactions (BTR)
- 103 • National Cancer Institute Common Terminology Criteria for Adverse Events
- 104 (NCI-CTCAE)
- 105 • Skin prick test (SPT)
- 106 • Intradermal test (IDT)
- 107 • Serum tryptase (sT)
- 108 • Drug provocation test (DPT)
- 109 • Intensive care unit (ICU)
- 110

Text:

INTRODUCTION

The diagnosis of neoplastic malignancies and inflammatory diseases has been increasing in the last years. This results in a larger number of patients being exposed to antineoplastic and biological agents for long periods of time and frequently in repeated courses, leading to a parallel increase in the incidence of drug hypersensitivity reactions (DHRs)¹⁻⁴. DHRs may compromise the use of first-line treatments for severe diseases leading to the use of alternative drugs that may be more toxic or less effective, influencing the survival prognosis. Thus, appropriate long-term management of DHRs is essential⁵⁻¹⁸.

To overcome this problem, rapid drug desensitization (RDD) has become a suitable option for these patients to receive the drug of choice. It has been used for numerous drugs, including chemotherapeutic (CMT) and biologic agents (BA) inducing a transient state of tolerance to the drug that triggered the previous DHR⁵⁻¹⁸. When performed by expert physicians it is a cost-effective procedure that preserves the original survival prognosis of the patient and has proven to be safe and effective in the management of DHRs^{5-10,12-19}.

Although different rapid drug desensitization (RDD) protocols have been described, a 12-step protocol using three bag with sequential dilutions of the drug^{8,9,13,20,21} developed by Castells et al.⁹ is nowadays the most widely used. However, faster protocols with one or two dilutions have been described^{14,22-26}. Currently, high-precision pumps allow precise infusion rate of very low doses enabling the initiation of RDD with the standard drug concentration without dilution, as it has been demonstrated in other contexts apart from RDDs in terms of safety, control of low doses, the infusion rate and a less need of drug manipulation²⁷⁻²⁹.

The aim of this study was to compare the efficacy and safety of a one-bag dilution protocol (1DP) using a high-precision pump used at our institution between 2017-2019, compared to the three-bag dilution protocol (3DP) used between 2014-2016 for RDD procedures with chemotherapeutic (CMT) and biologic agents (BA) through a retrospective observational study.

METHODS:

Study population and design

A retrospective, observational, cross-sectional study was performed including all patients from 2014 to 2019 who had been referred to our Allergy Section after a drug hypersensitivity reaction (DHR) to chemotherapeutic or biological agents (CMT or BA). Demographic characteristics and clinical data of patients were registered.

Risk assessment

Only immediate reactions occurring during the infusion or within one hour after completion were considered for rapid drug desensitization (RDD).³⁰ The severity of reactions was classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0³¹ as well as Brown's anaphylaxis severity grading (**Table I**)³².

Patients' baseline risk was classified as high or moderate/low risk depending on the severity of the initial reaction, baseline state of the patients in relation to their disease (mainly neoplastic), number of associated comorbidities (severe ischemic cardiomyopathy, uncontrolled hypertension, neurologic stroke, chronic obstructive pulmonary disease or COPD, and diabetes), medications taken by the patient such as beta-blockers or angiotensin-converting enzyme inhibitors (ACE inhibitors) where

exposure or breakthrough reactions might provoke situations beyond medical control, and the discretion of the treating clinician³³.

In our study patients with DHR with a grade of severity I (Brown's or NCI-CTCAE v5.0), with no severe comorbidities (for instance, cardiovascular or neurological strokes or other diseases not stabilized) and a good performance status were classified as basal low risk. With the increase of severity of DHR, comorbidities or a worsening of performance status, the basal risk increased to medium/severe (when the grade of severity was III with any severe comorbidity).

The risk stratification and the assessment of the BTR was always performed by the same three allergists, trained for these specific procedures, in order to avoid variability in the classification criteria of the patients.

After assessing the risk, a coordinated decision between the patient, the oncologist and the allergist was required to decide upon the indication of a drug provocation test (DPT) or a rapid drug desensitization (RDD).

Diagnostic approach to assess candidate patients for rapid drug desensitization (RDD)

Skin testing with the culprit drug was performed at least 2-4 weeks after the drug hypersensitivity reaction (DHR), at the same day of RDD or drug provocation test (DPT) if considered. Skin tests (skin prick test and/or intradermal test) were performed using non-irritating published concentrations^{11,34,35} following the method described by European Academy of Allergy and Clinical Immunology and the European Network for Drug Allergy³⁶, or in their absence, with 1:100-1:10 dilutions of the commercial presentation of each drug. To test whether these drug concentrations were irritating, they were tested in 5 control patients receiving and tolerating the same drug if they accepted and signed an informed consent. Skin test concentrations used in this study are

summarized in **Table II**. Results were read following standardized interpretation³⁶. Serum tryptase levels (sT) were determined during the reaction (initial determination during the first hour of the reaction, second at 2-6 hours) and at baseline (at least, 48 hours after the reaction), in order to detect a possible underlying mast cell activation syndrome. An increase in serum tryptase over the cut-off value (11.4 µg/L) (ImmunoCAPTM, Thermo-Fisher Scientific, Sweden) as well as a rise of a 20% + 2 µg/L of the basal serum tryptase was considered suggestive of mast cell activation^{37,38} and those patients were considered candidates for RDD (**Figure 1**). The blood for serum tryptase determinations were obtained at oncology day unit following the emergency protocol in case of suspicion of drug hypersensitivity reaction (DHR) by trained nurses. Drug provocation tests (DPT) are considered the gold standard to confirm or exclude the diagnosis of DHRs, being an important tool to confirm or exclude allergic reactions to CMT and BA^{21,39-41}. In this study, patients with normal basal serum tryptase levels (sT), absence of rise in sT during DHR and a basal medium/low risk (defined by the comorbidities, performance status and initial hypersensitivity reaction of the patient) underwent a DPT, and when positive, they were considered candidates for RDD (**Figure 1**). Drug provocation test to chemotherapeutic and biological agents were performed following procedures already published⁴². Specific anti-alpha-gal-IgE (ImmunoCAPTM, Thermo-Fisher Scientific, Sweden) was also assessed in patients reporting an immediate DHR with cetuximab.

Desensitization protocols

A coordinated decision between the patient, the oncologist and the allergist was ~~were~~ required to decide upon the indication of a drug provocation test (DPT) or a rapid drug desensitization (RDD), taking into account the clinical reaction, skin test results,

211 mobilization of serum tryptase during the reaction and the basal risk of the patient
212 ^{23,32,37,38,43–47}.

213 RDD was conducted in patients who presented an immediate DHR and, positivity in
214 skin test (ST) with the culprit drug and/or rise in serum tryptase levels independently of
215 their basal risk, after the patient signed an informed consent, if indicated. RDD was also
216 performed in case of patient basal-high risk and negative or not performed skin test
217 and/or serum tryptase determination. Desensitization was not performed if the reaction
218 was suspected by a delayed immune-mediated reaction, in patients with negative drug
219 provocation test (DPT) or those who did not need additional administration of the drug.
220 We offered a desensitization protocol to the 8 patients with a positive challenge test, and
221 6 of them underwent to a RDD with no incidences and for the other two patients the
222 oncologist decided to change to an alternative drug since the expected response was
223 deemed as limited, as it is summarized in **Figure 1**.

224 The RDD protocol was performed at an allergy-procedure-dedicated-place inside the
225 oncology day unit, except for those patients with extremely severe DHRs or very high
226 basal risk, which were treated in the Intensive Care Unit (ICU). An allergist supervised
227 all procedures until at least two RDD were uneventful, in which case they were
228 subsequently supervised by allergy trained oncology day unit nurses, with the allergist
229 on call. The allergist on call reviews the patients on RDD that are scheduled daily.

230 Between 2014 and 2016, a three-bag-dilution-protocol (3DP) (1:100, 1:10, 1:1) of the
231 culprit drug was used. The mean number of steps was 10, according to previously
232 published protocols based on *in vitro* and *in vivo* experience ^{8,21}. There were minor
233 modifications in the protocol in selected cases, adding steps or increasing time from 15
234 to 20 minutes per step, depending on the drug, breakthrough reactions during RDD and
235 risk stratification.

Between 2017 and 2019 our desensitization protocols were changed taking advantage of the options of automatic high precision pumps (InfusomatTM Space, Braun, Germany) that allow the use of drug dilution administration rates from 0.1 mL/h to reduce procedure time, to minimize errors and to simplify preparation by the pharmacists. Thus, one-bag-dilution-protocol (1DP) was used at usual concentration indicated by manufacturers²⁴. The number of steps and speed administration drug in 1DP was the same as used in 3DP, but the high precision pump allowed us to remove the necessity of changing bags. As in 3DP, the number of steps for the RDD was individualized depending on the drug, and the risk assessment with a mean of 10 steps with 15 minutes in the first nine steps. The infusion system was primed with the drug to keep an accurate control of the administered dose from the beginning. Dextrose 5% in water or saline serum (according to the manufacturer instructions) was infused via a three-way stopcock in a rate of 200 mL/h to lower the concentration of the undiluted solution as well as to ensure the infusion of the drug specially in the first steps. The infusion rate was duplicated every 15 minutes until the rate recommended by the manufacturer was achieved. In **Table III**, the two different protocols (3DP vs 1DP) for carboplatin desensitization, with target dose for 771 and 473mg, are shown as an example.

Premedication with dexamethasone, ondansetron, ranitidine or other drugs were administered before RDD following the manufacturer's instructions for each drug⁴⁸. Further premedication prescribed by the allergist were dexchlorpheniramine or additional corticosteroids, which were administered in some patients according to clinical symptoms, severity of the reaction or drug breakthrough reactions (BTR) in previous desensitizations. In our experience steroids are a useful immediate premedication especially in non IgE mediated reactions, when a cytokine release syndrome reaction with biological or chemotherapeutic drugs is suspected (elevated IL-6 levels and normal

tryptase during the reaction). Other premedication drugs, such as montelukast or aspirin were used at initial procedures but were progressively abandoned due to the lack of efficacy observed in our patients⁴⁹.

Outcomes

The primary outcome was the rate of patients completing drug administration with any of the two protocols. Secondary outcomes were the number and the severity of breakthrough reactions (BTR) as well as the duration of the RDD according to both protocols.

Ethical statement

The study has been approved by Vall d'Hebron University Hospital Ethics Committee (IRB number: PR(AG)352-2019). All patients were informed and signed an informed consent.

Statistical analysis All continuous variables are expressed as mean $\pm$ standard deviation (SD), and exact 95% confidence interval (CI) is indicated. A χ^2 and Fisher's exact test was used to compare the incidence and severity of BTR, and the completion rate of two different protocols. Data was collected and analyzed with SPSS version 25.0 (SPSS Inc., Chicago, Ill., USA). A p value ≤ 0.05 was considered statistically significant.

RESULTS:

Patient characteristics:

Between 2014 and 2019, 180 patients with DHRs to chemotherapeutic or biological agents were referred to our department. The diagnostic/therapeutic flowchart is shown in **Figure 1**.

After the allergy workup, 157 patients accomplished criteria to undergo at least 1 RDD (137 women/20 men, mean age of 60.44 ± 12.6 years, range 19-82 years); 148 patients were treated for malignancies, 8 for inflammatory diseases and 1 for a lysosomal disease. The severity of the initial reaction was moderate to severe in 64.32% (Brown's grade II-III) and 70% (NCI-CTCAE v5.0 II-IV) of the subjects while 35.68% (Brown's grade I) and 30% (NCI-CTCAE v5.0 I) of patients presented a mild reaction as is shown in **Table I**.

Skin tests and drug provocation tests (DPT):

Skin test and DPT results are displayed in **Table IV**. A total of 151 patients underwent skin testing with a rate of positivity of 46.4%. Platinum salt agents had the highest rate of positive skin test (70-100%) while monoclonal antibodies yielded positive results only in 15% of patients. There was one positive intradermal test (IDT) to cetuximab in a patient with a positive specific IgE for alpha-gal.

Rapid drug desensitization (RDD) outcomes:

We offered a desensitization protocol to all patients who meet criteria but in 8 cases either the patients, or the responsible oncologist rejected the RDD. In total, 639 desensitization procedures were performed in 157 patients. Of these, 48 patients underwent 205 RDD with 3DP and 109 patients underwent 434 RDD with 1DP (**Table V**). Gynecological malignancies were the most frequent condition and platinum salts were the most frequent culprit drugs followed by taxanes.

Of 639 RDD undertaken, 636 were successfully accomplished, giving a success rate of 99.5%. Regarding the other three, the procedure was discontinued due to the severity of breakthrough reactions (BTR) and the revocation of the consent by the patient in the second session of desensitization after extensive explanations about risk-benefit with their oncologist. There were two patients following 1DP and one 3DP. The distribution comparing the severity of BTR during desensitization with the two protocols is shown in **Figure 2**, with no significant differences ($p=.80$). No BTR occurred in the first RDD procedure in a 52% (3DP) and 51 % (1DP) of the RDDs. Most BTR were mild, showing no statistical differences between protocols. BTR were less severe compared to the initial reaction as shown in **Figure 3**. Breakthrough reactions (BTR) occurred mainly during the final steps of the procedure. Considering the pharmacological group, platinum salts showed the highest rate of BTR (57%) in contrast with taxanes that showed the lowest (18%).

Both RDD protocols showed a decrease of BTR after repeated cycles. Breakthrough reactions (BTR) persisted after the first RDD in 45 patients (33 platinum salts, 5 rituximab, 3 taxanes, 1 cetuximab, 1 doxorubicin, 1 irinotecan and 1 trastuzumab). The severity of reactions in most cases was mild (77.7%) and controlled effectively with antihistamines and corticosteroids. Grade II-III reactions (Brown's classification) occurred in 10 of 45 of patients (22.2%) being 7 of them due to platinum salts, 1 to doxorubicin, 1 to docetaxel and 1 to rituximab and requiring the use of adrenaline. No admissions to ICU or hospitalization were required and no deaths were recorded.

Rapid drug desensitization (RDD) duration:

The desensitization duration with 1DP was shorter than 3DP in all pharmacological groups (195-290 min vs 255-349 min respectively). For example, in the case of carboplatin it was 154 minutes shorter than that with the 3DP ($P < .05$) as shown in

Table III. Oxaliplatin with 1DP showed a reduction of 35 minutes with respect to 3DP (220 min vs 255 min), paclitaxel about 48 minutes (290 min vs 338 min) and rituximab of 45 minutes (254 min vs 300 min).

DISCUSSION:

This is the largest study from a single center comparing RDD protocols with three-bag dilutions (3DP) (n=48 patients) and one-bag dilution (1DP) (n=109 patients), collecting data from 6 years (2014-2019) of 639 RDD to CMT and BA, with an overall success rate of 99.5%.

Vidal et al.²² published 58 procedures in 12 patients who were desensitized with a 1DP, showing a safety and success rate similar to 3DP. Moreover, in 2020, Lee et al.²⁵ also showed that 1DP was a non-inferior option compared to multi-bag RDD in 49 patients with paclitaxel DHRs in terms of efficacy and safety.

Other studies have also assessed the use of 1DP in RDD⁵⁰. One of the largest series was published by Pérez-Rodríguez et al.¹⁰, on 490 RDD in 90 patients using a 1DP, with optimal outcomes. Moreover, Chung SJ et al.²⁶, reported in 2018 the use of 1DP applied to 36 patients with DHRs due to platinum salts. Of 175 desensitization procedures, all cases were successfully completed. Moreover, there are some case reports of successful RDD to different drugs using 1DP protocol^{24,45}.

Although this is not the first study that compares multiple-bag against one-bag dilution, our study reinforces the results of previously published articles comparing both protocols. In addition, our group has described for the first time the good efficacy and tolerability of a 1DP in RDD for etoposide and obinituzumab.

The two main advantages of 1DP are time-reduction of the procedure and optimization of risk-management. RDD duration is clearly shortened as shown in the current study,

which entails an improvement for the patient and for the health-care resources. This approach simplifies logistic management, reducing the risk of possible errors without compromising the safety, efficacy, and tolerability of the process.

We want to point out that currently, characteristics of high-precision pumps allow us precise infusion rate of very low doses. The number of steps and speed administration drug in our 1DP was the same that the used in 3DP. We only prime the infusion system with the drug to keep an accurate control of the administered dose from the beginning and added dextrose 5% in water or saline serum (according to the manufacturer instructions) via a three-way stopcock in a rate of 200 mL/h to ensure the infusion in the patient of the chemotherapeutic or biological drug especially in the first steps.

Skin tests were performed systematically in all patients to assess the involvement of an underlying IgE-mediated reaction. The sensitivity and specificity of skin testing in platinum salts range from 40% to 80%^{9,51,52}. Although the aim of our study was not to analyze the diagnostic performance of skin tests, prevalence of platinum salts positive skin tests was like previously reported (74.6%). Some studies have reported skin testing with taxanes to be of limited value^{9,53}. As the majority of patients reacted to these drugs on the first or second infusion, an IgE-mediated mechanism seems unlikely, suggesting other possible mechanisms, such as complement activation by reactive metabolites, direct mast cell/basophil or macrophage activation^{52,54}. Our rate of positive skin tests to taxanes (docetaxel 16.1% and paclitaxel 12.1%) are similar to previous reports⁵⁵, in contrast with Picard et al.²³ from Boston, USA, who report positivity rates for paclitaxel of 71% and for docetaxel of 89%. Skin tests to monoclonal antibodies resulted positive in only 15% of cases. Data on non-irritating concentrations for monoclonal antibody skin testing is scarce, and some authors are concerned by costs⁵⁶.

A strategy to overcome this latter limitation is performing the skin tests on the day when the RDD is scheduled and prepare the diagnostic dilutions from the treatment solution. Drug provocation test (DPT) is the gold standard criterion to confirm or rule out DHRs, especially when skin and serum IgE results are negative, unavailable, or not validated³⁰. Some authors recommend its use also in DHRs to CMT and BA in selected cases before performed RDD^{11,21,57}. In our hospital, the use of DPT is a common approach. However, in this study a limited number of DPT (N=29, summarized in **Figure 1** and **Table IV**) were performed since most patients presented severe reactions with positive skin test and/or elevated serum tryptase levels during initial reactions. None of the 21 patients with negative provocation challenges reacted upon additional administrations. We did not carry out DPT in cases of high-risk patients due to clinical status, uncontrolled comorbidities or very severe reactions and directly performed RDD. Therefore, there may have been several “false-positive” diagnoses. Breakthrough reactions (BTR) occurred in about half of the patients, independent of which protocol was used. However, most of them were mild and this rate decreased with subsequent RDD, as described in other studies^{9,21,58}. There are several limitations in this study. First, although this study included 639 RDD procedures and a high number of patients, it is a single-center study. In addition, this is a retrospective study and although the two different protocols were performed in very similar conditions, it was not randomized. Also, due to the observational design, the use of premedication was not standardized. Finally, only a small number of DPT were performed to establish the definitive diagnosis of DHR. In conclusion, rapid drug desensitization with 1DP to CMT and BA seems safe, effective, and well tolerated in a selected population of patients. Moreover, 1DP reduces

the time required for RDD and simplifies the logistics. Further studies are needed to validate its use in high-risk patients as well as in other patient cohorts.

Acknowledgments:

This research would not have been possible without the collaboration from our patients, the nurses from Oncology Day Unit, the Oncology Department, the Pharmacology Department and the Intensive Care Medicine Department from Hospital Universitari Vall d'Hebron.

References:

1. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): A population-based study. *Lancet Oncol.* 2012; 13(8):790-801
2. Muallaoglu S, Disel U, Mertsoylu H, Besen A, Karadeniz C, Taner Sumbul A, et al. Acute infusion reactions to chemotherapeutic drugs: A single institute experience. *J BUON.* 2013; 18(1):261-7
3. Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: Data mining of the public version of the FDA adverse event reporting system, AERS. *J Exp Clin Cancer Res.* 2011 Oct 5; 30(1):9
4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65:87-108.
5. Bonamichi-Santos R, Castells M. Diagnoses and Management of Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: Reactions to Taxanes and Monoclonal Antibodies. *Clin Rev Allergy Immunol.* 2018 Jun; 54(3):375-385
6. Bonamichi-Santos R, Castells M. Desensitization for Drug Hypersensitivity to Chemotherapy and Monoclonal Antibodies. *Curr Pharm Des.* 2016;22:6870-80.
7. Lopez-Gonzalez P, Madrigal-Burgaleta R, Carpio-Escalona LV, Bernal-Rubio L, Guerra E, Berges-Gimeno MP, et al. Assessment of Antihistamines and Corticosteroids as Premedication in Rapid Drug Desensitization to Paclitaxel: Outcomes in 155 Procedures. *J Allergy Clin Immunol Pract.* 2018;6:1356-62.
8. Castells M, Del Carmen Sancho-Serra M, Simarro M. Hypersensitivity to antineoplastic agents: Mechanisms and treatment with rapid desensitization. *Cancer Immunol Immunother.* 2012; 61(9):1575-84
9. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol.* 2008;122:574-80.

- 444 10. Pérez-Rodríguez E, Martínez-Tadeo JA, Pérez-Rodríguez N, Hernández-Santana
445 G, Callero-Viera A, Rodríguez-Plata E, et al. Outcome of 490 Desensitizations to
446 Chemotherapy Drugs with a Rapid One-Solution Protocol. *J Allergy Clin Immunol*
447 *Pract.* 2018; 6(5):1621-1627
- 448 11. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A,
449 Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of
450 hypersensitivity to antineoplastic and biological agents: Value of diagnostic tools
451 prior to desensitization. *Allergy.* 2015 Jul; 70(7):784-94
- 452 12. Ureña-Tavera A, Zamora-Verduga M, Madrigal-Burgaleta R, Angel-Pereira D,
453 Berges-Gimeno MP, Alvarez-Cuesta E. Hypersensitivity reactions to racemic
454 calcium folinate (leucovorin) during FOLFOX and FOLFIRI chemotherapy
455 administrations. *J Allergy Clin Immunol.* 2015; 135:1066–7.
- 456 13. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-
457 Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and
458 desensitization to antineoplastic agents: outcomes of 189 procedures with a
459 new short protocol and novel diagnostic tools assessment. *Allergy.*
460 2013;68:853–61.
- 461 14. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Guillen-
462 Ponce C, Sanz ML, Alvarez-Cuesta E. Desensitizing oxaliplatin-induced fever: A
463 case report. *Journal of Investigational Allergology and Clinical Immunology.*
464 2013. *J Investig Allergol Clin Immunol.* 2013; 23(6):435-6.
- 465 15. Angel-Pereira D, Berges-Gimeno MP, Madrigal-Burgaleta R, Ureña-Tavera MA,
466 Zamora-Verduga M, Alvarez-Cuesta E. Successful rapid desensitization to
467 methylprednisolone sodium hemisuccinate: a case report. *J Allergy Clin*
468 *Immunol Pract.* 2014; 2(3):346-8.
- 469 16. Solano-Solares E, Madrigal-Burgaleta R, Carpio-Escalona L V, Bernal-Rubio L,
470 Berges-Gimeno MP, Alvarez-Cuesta E. Chemotherapy in Mastocytosis:
471 Administration Issues, Hypersensitivity, and Rapid Drug Desensitization. *J*
472 *Investig Allergol Clin Immunol.* 2017 ;27:315–7.
- 473 17. Alvarez-Cuesta E, Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D.
474 Rapid desensitization to chemotherapy and monoclonal antibodies is effective
475 and safe. *Reply. Allergy.* 2013;68:1483–4.
- 476 18. Madrigal-Burgaleta R. Hipersensibilidad a los agentes antineoplásicos y
477 fármacos biológicos: un nuevo paradigma diagnóstico y terapéutico. [Doctoral
478 Thesis] Universidad de Alcalá; 2017.
- 479 19. Berges-Gimeno MP, Carpio-Escalona L V., Longo-Muñoz F, Bernal-Rubio L,
480 Lopez-Gonzalez P, Gehlhaar P, et al. Does rapid drug desensitization to
481 chemotherapy affect survival outcomes. *J Investig Allergol Clin Immunol.* 2020;
482 30:254–63.
- 483 20. Kendirlihan R, Gümüşburun R, Çerçi P, Özbek E, Altiner S, Çelebi Sözüner Z, et al.
484 Rapid Drug Desensitization with Chemotherapeutics (Platins, Taxanes, and
485 Others): A Single-Center Retrospective Study. *Int Arch Allergy Immunol.* 2019;
486 179:114–22.
- 487 21. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV,
488 Gehlhaar P, Alvarez-Cuesta E. A Large Single-Hospital Experience Using Drug
489 Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to
490 Antineoplastic and Biological Agents. *J allergy Clin Immunol Pract.* 2019; 7:618–

- 32.
22. Vidal C, Méndez-Brea P, López-Freire S, Bernárdez B, Lamas MJ, Armisen M, et al. A modified protocol for rapid desensitization to chemotherapy agents. *J Allergy Clin Immunol Pract.* 2016;4:1003–5.
23. Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol.* 2016; 137:1154-1164.
24. Pérez-Rodríguez E, Hernández-Pérez MÁ, Martínez-Tadeo JA. Successful desensitization to natalizumab using a 1-solution protocol. *Ann Allergy Asthma Immunol.* 2017;118:113–4.
25. Lee JH, Moon M, Kim YC, Chung SJ, Oh J, Kang DY, et al. A One-Bag Rapid Desensitization Protocol for Paclitaxel Hypersensitivity: A Noninferior Alternative to a Multi-Bag Rapid Desensitization Protocol. *J Allergy Clin Immunol Pract.* 2019;S2213-2198(19)30904-3.
26. Chung SJ, Kang SY, Kang RY, Kim YC, Lee KH, Kim TY, et al. A new non-dilution rapid desensitization protocol successfully applied to all-grade platinum hypersensitivity. *Cancer Chemother Pharmacol.* 2018;82:777–85.
27. Weinger MB, Kline A. Reflections on the current state of infusion therapy. *Biomed Instrum Technol.* 2016 ;50:253–62.
28. Murdoch LJ, Cameron VL. Smart infusion technology: a minimum safety standard for intensive care?. Vol. 17, *British journal of nursing* (Mark Allen Publishing). MA Healthcare London ; 2008. p. 630–6. Available from:
29. Jani YH, Chumbley GM, Furniss D, Blandford A FB. The Potential Role of Smart Infusion Devices in Preventing or Contributing to Medication Administration Errors: A Descriptive Study of 2 Data Sets. *J Patient Saf.* 2020.
30. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. *Allergy.* 2014;69:420–37.
31. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Internet]. 2017. Available from: <https://www.meddra.org/>[cited 2019 Dec 24].
32. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol.* 2004;114:371–6.
33. Hong DI, Madrigal-Burgaleta R, Banerji A, Castells M, Alvarez-Cuesta E. Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel? *J Allergy Clin Immunol Pract.* 2020; 8(9):2907-2915
34. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs *J Allergy Clin Immunol Pract.* 2020 Oct; 8(9S):S16-S116.
35. Gómez-Duque M, Sala-Cunill A, Farriols A, Cardona V, Luengo O. Safe and Time-Saving Desensitization Protocol to Intravenous Etoposide. *J Allergy Clin Immunol Pract* 2016. p. 793–4.
36. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45–51.
37. Brown SGA, Blackman KE, Heddle RJ. Can serum mast cell tryptase help diagnose anaphylaxis? *EMA - Emerg Med Australas.* 2004;16:120–4.
38. Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SGA, Emergency

- Department Anaphylaxis Investigators. Elevated serum cytokines during human anaphylaxis: Identification of potential mediators of acute allergic reactions. *J Allergy Clin Immunol*. 2009; 124:786-92.
39. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. *Allergy*. 2003; 58(9):854-63
 40. Martí-Garrido J, Vázquez-Revuelta P, Leonart-Bellfill R, Molina-Mata K, Muñoz-Sánchez C, Madrigal-Burgaleta R. Pilot experience using drug provocation testing for the study of hypersensitivity to chemotherapy and biological agents. *J Investig Allergol Clin Immunol*. 2020 ;31.
 41. Vázquez-Revuelta P, Martí-Garrido J, Molina-Mata K, Leonart-Bellfill R, Rey-Salido Pharm M, Madrigal-Burgaleta R. Delabeling Patients from Chemotherapy and Biologics Allergy: Implementing Drug Provocation Testing. *J Allergy Clin Immunol Pract*. 2020 Nov 24; S2213-2198(20)31242-3
 42. Madrigal-Burgaleta R, Vazquez-Revuelta P, Marti-Garrido J, Leonart R, Ali FR, Alvarez-Cuesta E. Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals. *Curr Treat Options Allergy*. 2020; 7:1–13.
 43. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol*. 2012;129:443–7.
 44. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68:702–12.
 45. Hong DI, Bankova L, Cahill KN, Kyin T, Castells MC. Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. *Expert Rev Clin Immunol*. 2012; 8:43–52; quiz 53–4.
 46. Isabwe GAC, Garcia Neuer M, de las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. *J Allergy Clin Immunol*. 2018;142:159-170.
 47. Giavina-Bianchi P, Aun MV, Galvão VR, Castells M. Rapid Desensitization in Immediate Hypersensitivity Reaction to Drugs. *Curr Treat Options Allergy*. 2015;2:268–85.
 48. de Las Peñas R, Blasco A, De Castro J, Escobar Y, García-Campelo R, Gúrpide A, et al. SEOM Clinical Guideline update for the prevention of chemotherapy-induced nausea and vomiting (2016). *Clin Transl Oncol*. 2016;18:1237–42.
 49. Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol*. 2009; 102:155–60.
 50. Park HK, Lee SJ, Kim S, Lee JM, Hong DG. Does Carboplatin Rapid Desensitization Change Its Adverse Drug Reactions Other than Hypersensitivity and Efficacy in Patients With Ovarian Cancer? *Allergy Asthma Immunol Res*. 2020;12:1046–59.
 51. Lax T, Long A, Banerji A. Skin Testing in the Evaluation and Management of Carboplatin-Related Hypersensitivity Reactions. *J Allergy Clin Immunol Pract*. 2015;3(6):856-62

- 584 52. Castells M. Rapid Desensitization for Hypersensitivity Reactions to Medications.
585 Immunol Allergy Clin North Am 2009 Aug;29(3):585-606
- 586 53. Feldweg AM, Lee C-W, Matulonis UA, Castells M. Rapid desensitization for
587 hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol
588 used in 77 successful treatments. Gynecol Oncol . 2005; 96:824–9.
- 589 54. Picard M, Castells MC. Re-visiting Hypersensitivity Reactions to Taxanes: A
590 Comprehensive Review. Clin Rev Allergy Immunol. 2015;49(2):177-91
- 591 55. Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, Cernadas J, et al. Role
592 of Skin Tests in the Diagnosis of Immediate Hypersensitivity Reactions to
593 Taxanes: Results of a Multicenter Study. J Allergy Clin Immunol Pract . 2019;
594 7:990–7.
- 595 56. Hong D, Sloane DE. Hypersensitivity to monoclonal antibodies used for cancer
596 and inflammatory or connective tissue diseases. Ann Allergy Asthma
597 Immunol. 2019;123(1):35-41
- 598 57. Giavina-Bianchi P, Patil SU, Banerji A. Immediate Hypersensitivity Reaction to
599 Chemotherapeutic Agents. J Allergy Clin Immunol Pract. 2017;5:593–9.
- 600 58. Brennan PJ, Bouza TR, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions
601 to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J
602 Allergy Clin Immunol. 2009;124:1259–66.
603

Table I: Distribution of initial hypersensitivity reactions according to Brown's and NCI-CTCAE v.5 classification of 157 patients desensitized.

	CLASSIFICATIONS OF THE INITIAL REACTIONS								
	BROWN			NCI-CTCAE v.5					
DRUG	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III	Grade IV	Grade V	TOTAL
Agalsidase-Beta	0	0	1	0	0	1	0	0	1
Cetuximab	1	5	1	2	4	1	0	0	7
Cyclophosphamide	1	0	0	0	1	0	0	0	1
Docetaxel	1	5	0	1	3	2	0	0	6
Doxorubicine	3	3	0	2	3	1	0	0	6
Etoposide	0	2	0	0	2	0	0	0	2
Carboplatin	22	13	15	18	4	26	2	0	50
Oxaliplatin	17	4	1	15	2	5	0	0	22
Cisplatin	0	1	2	0	0	3	0	0	3
Paclitaxel	5	18	10	4	14	15	0	0	33
Irinotecan	4	2	0	3	2	1	0	0	6
Nivolumab	0	1	0	0	1	0	0	0	1
Obinutuzumab	0	0	1	0	0	1	0	0	1
Rituximab	2	9	3	2	6	6	0	0	14
Trastuzumab	0	4	0	0	3	1	0	0	4
Total (%)	56 (35.68%)	67 (42.67%)	34 (21.65%)	47 (30%)	45 (28.7%)	63 (40%)	2 (1.3%)	0	157

605 **Table II:** Skin test concentrations used during allergological work-up.

Agent	Skin prick test	Intradermal test
Carboplatin	10mg/ml	1mg/ml (1:10 dilution)
Oxaliplatin	5mg/ml	0.5mg/ml (1:10 dilution)
Cisplatin	1mg/ml	0.1mg/ml (1:10 dilution)
Docetaxel	10mg/ml	1mg/ml (1:10 dilution)
Paclitaxel	6mg/ml	0.6mg/ml (1:10 dilution)
Rituximab	10mg/ml	1mg/ml (1:10 dilution)
Cetuximab	5mg/ml	5mg/ml
Trastuzumab	21mg/ml	2.1mg/ml (1:10 dilution)
Nivolumab	NA (1:1 dilution)	NA (1:100 and 1:10 dilution)
Obinutuzumab	NA (1:1 dilution)	NA (1:100 and 1:10 dilution)
Cyclophosphamide	10mg/ml	1mg/ml 1mg/ml (1:10 dilution)
Doxorubicine	ND (vesicant)	ND (vesicant)
Etoposide	20mg/ml	2mg/ml
Irinotecan	2mg/ml	0.2mg/ml 1mg/ml (1/10 dilution)
Agalsidase-Beta	NA (1:1 dilution)	NA (1:100 and 1:10 dilution)

606 NA,Concentration not available; ND Not done

607 **Table III:** Comparison of two protocols for Carboplatin desensitization.

608 **Table IIIA)** 3-bag, 10-step protocol (dosing 771 mg of carboplatin diluted at three
 609 different concentrations) using a high-precision automatic pump (InfusomatTM Space,
 610 Braun, Germany).

Total dose	771mg	Solution concentration	Total dose in each solution (mg)	Drug
Solution A	250 ml	0.016 mg/ml	4.0	Carboplatin
Solution B	250 ml	0.160 mg/ml	40.0	Carboplatin
Solution C	603 ml	1.22 mg/ml	740.15	Carboplatin

Step	Solution	Rate (ml/h)	Administered volume (ml)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	100	25	15	0.4	0.4
2	A	200	50	15	0.8	1.2
3	A	400	100	15	1.6	2.8
4	B	100	25	15	4	6.8
5	B	200	50	15	8	14.8
6	B	400	100	15	16	30.8
7	C	100	25	15	30.5	61.3
8	C	200	50	15	61	122.3
9	C	400	100	15	122	244.3
10	C	500	428	51	522.16	766.46

611

612

613 **Table IIIB)** A non-diluted one bag protocol, with 10 steps (dosing 473 mg of
 614 carboplatin diluted in 549 ml of volume, 0.86mg/ml) using a high-precision automatic
 615 pump (InfusomatTM Space, Braun, Germany).
 616

Step	Rate (ml/h)	Administered volume (ml)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	0.6	0.15	15	0.129	0.129
2	1.2	0.3	15	0.258	0.387
3	2.4	0.6	15	0.516	0.903
4	4.8	1.2	15	1.032	1.935
5	9.6	2.4	15	2.064	3.999
6	19.2	4.8	15	4.128	8.127
7	38.4	9.6	15	8.256	16.383
8	76.8	19.2	15	16.512	32.895
9	153.6	38.4	15	33.024	65.919
10	307.2	76.8	15	66.048	131.967
11	558	395.55	43	340.173	472.14

617

Table IV: Skin tests results of all patients and drug provocation tests results from the patients who met criteria to undergo a challenge test.

Drug	Skin Test N (% of positive)	Drug provocation Test N (% of positive)
Agalsidasa-Beta	1 (0%)	1 (100%)
Cetuximab	7 (14.3%)	3 (0%)
Cyclophosphamide	1 (100%)	ND
Docetaxel	6 (16.6%)	ND
Doxorubicine	ND	2 (0%)
Etoposide	2 (0%)	ND
Carboplatin	50 (70%)	5 (20%)
Oxaliplatin	22 (81.8%)	4 (50%)
Cisplatin	3 (100%)	3 (33.3%)
Paclitaxel	33 (12.1%)	4 (25%)
Irinotecan	6 (66.6%)	3 (33.3%)
Nivolumab	1 (0%)	ND
Obinutuzumab	1 (0%)	ND
Rituximab	14 (21.4%)	1 (100%)
Trastuzumab	4 (0%)	2 (0%)
Bentuximab	1 (0%)	1 (0%)

N, number of patients who met criteria for RDD; ND, not done

Table V: Distribution of total number of desensitizations procedures and type of rapid drug desensitization (one-bag or three-bag dilution) each patient received according to type of drug.

Type of Drug	Patients (n)	Rapid drug Desensitization procedures	Three-bag dilution (number of patients)	One-bag dilution (number of patients)
Agalsidasa-Beta	1	1	0	1
Cetuximab	7	30	2	5
Cyclophosphamide	1	3	1	0
Docetaxel	6	39	1	5
Doxorubicine	6	26	0	6
Etoposide	2	5	1	1
Carboplatin	50	150	18	32
Oxaliplatin	22	93	8	14
Cisplatin	3	6	1	2
Paclitaxel	33	134	12	21
Irinotecan	6	86	2	4
Nivolumab	1	2	1	0
Obinutuzumab	1	2	0	1
Rituximab	14	31	1	13
Trastuzumab	4	31	0	4
Total	157	639	48	109

Figure legends:

Figure 1: Rapid Drug desensitization's flowchart in our institution between 2014-2019 using both 3 and 1 dilution protocol.

RDD, rapid drug desensitization; DHRs, drug hypersensitivity reaction; DPT, drug provocation test; 3DP, Three-bag dilution protocol; 1DP, One-bag dilution protocol.

Figure 2: The severity of breakthrough reactions during desensitization comparing one and three-bag dilution procedures.

2a: Overall breakthrough reactions

BTR, Breakthrough reaction.

2b: Severity of breakthrough reactions according to the dilution protocol followed.

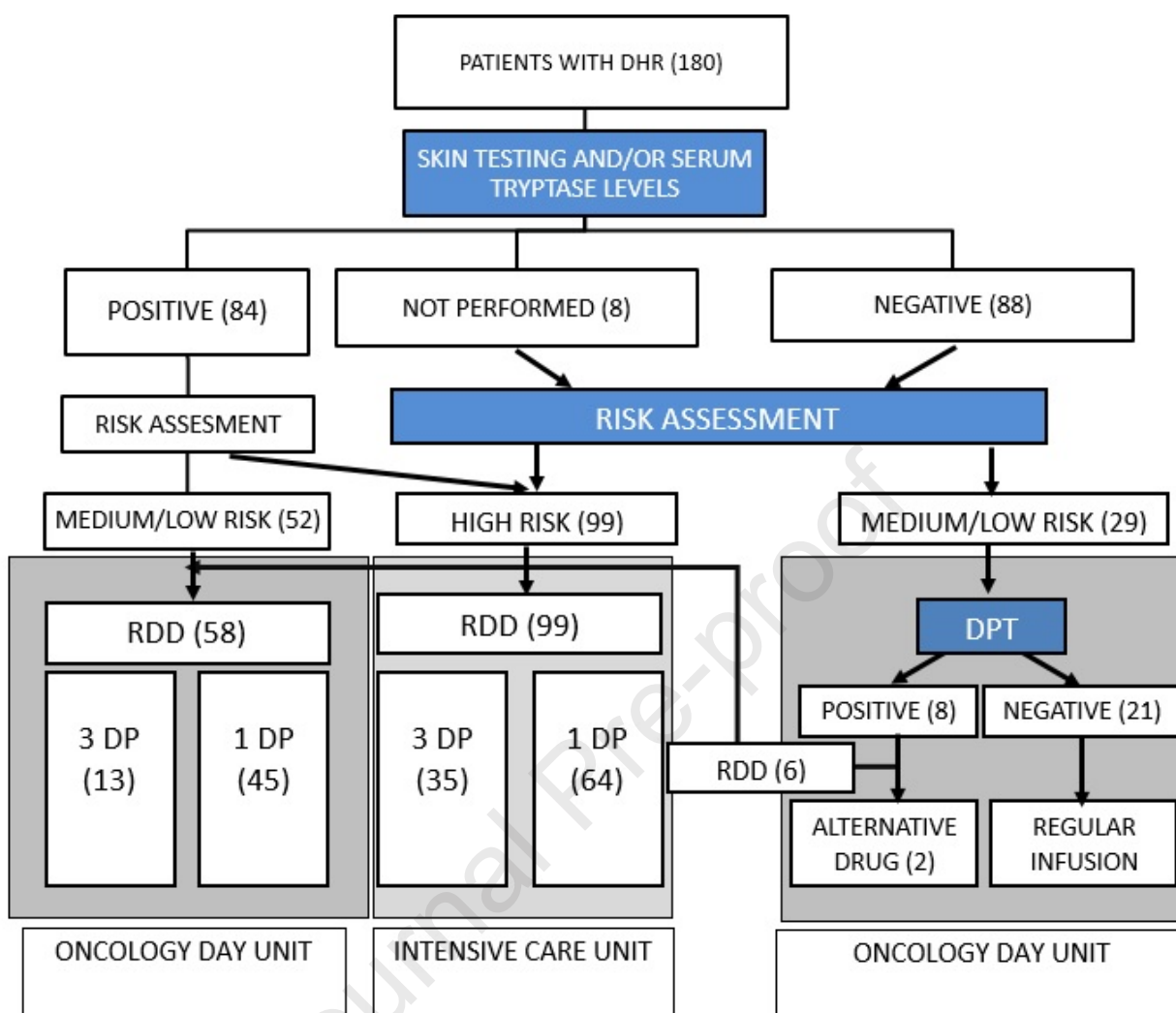
1DP, One-bag dilution protocol; 3DP, Three-bag dilution protocol.

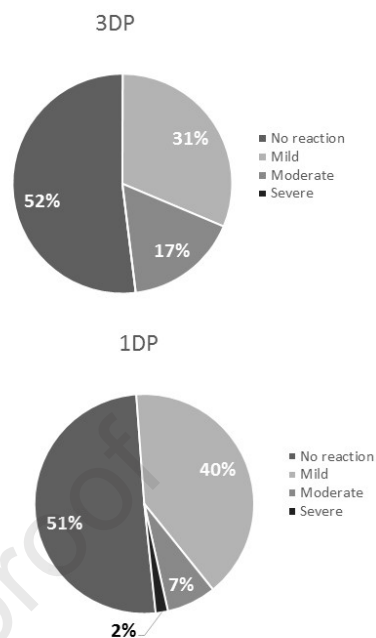
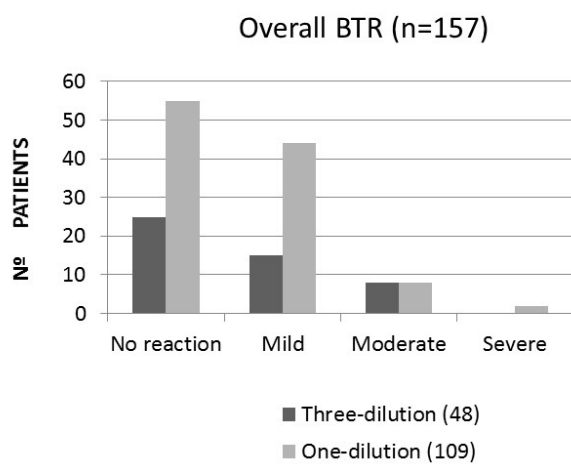
Figure 3: Severity of breakthrough reactions.

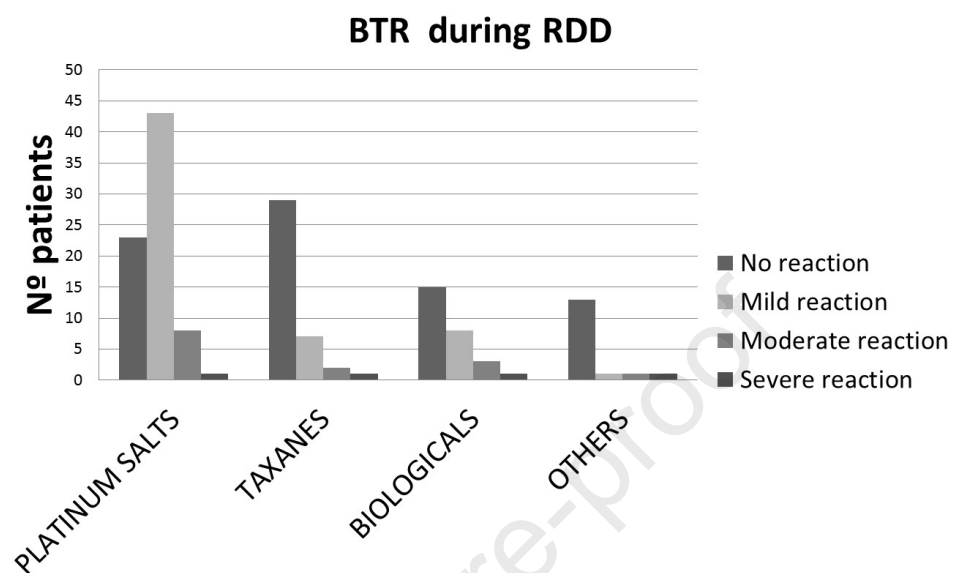
3a: Severity of breakthrough reactions according to the pharmacological group.

3b: Comparison between the severity of the initial reactions and the breakthrough reactions in the first RDD according to the pharmacological group and the dilution protocol followed.

RDD, rapid drug desensitization; BTR, breakthrough reactions.

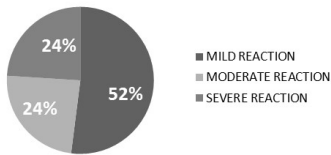




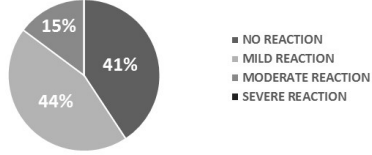


Platinum Salts: Initial Reactions

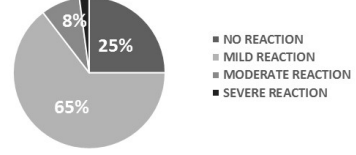
Nº of reactive patients: 75

**Platinum Salts: 3DP BTR**

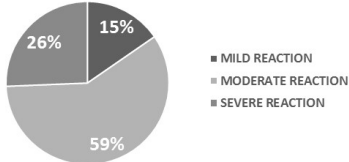
Nº of reactive patients 16/27

**Platinum Salts: 1DP BTR**

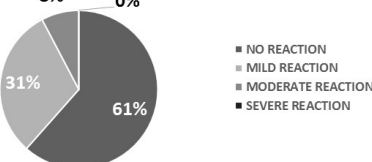
Nº of reactive patients 36/48

**Taxanes: Initial Reactions**

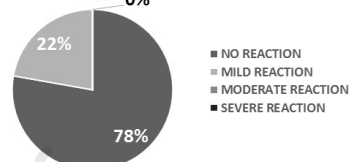
Nº of reactive patients: 39

**Taxanes: 3DP BTR**

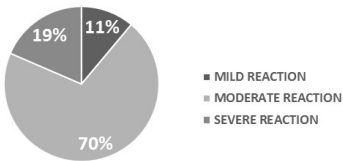
Nº of reactive patients: 5/13

**Taxanes: 1DP BTR**

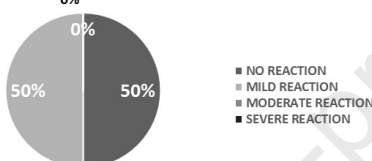
Nº of reactive patients: 5/26

**Biologicals: Initial Reactions**

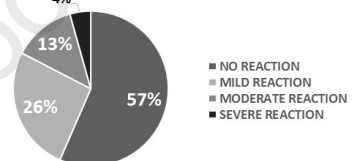
Nº of reactive patients: 27

**Biologicals: 3DP BTR**

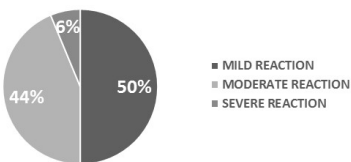
Nº of reactive patients: 2/4

**Biologicals: 1DP BTR**

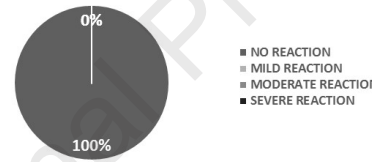
Nº of reactive patients: 10/23

**Others: Initial Reactions**

Nº of reactive patients: 16

**Others: 3DP BTR**

Nº of reactive patients: 0/4

**Others: 1DP BTR**

Nº of reactive patients: 3/12

