Hypersensitivity Reactions to Cancer Chemotherapy: Practical Recommendations of ARADyAL for Diagnosis and Desensitization

Running title: Management in cancer chemotherapy hypersensitivity


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ABSTRACT

Rapid drug desensitization (RDD) has allowed first line therapies in patients with drug hypersensitivity reactions (DHR) to chemotherapeutic drugs (ChD) including monoclonal antibodies (mAb). Desensitization is a safe and highly effective procedure, not only for IgE-mediated reactions but also for those mediated by non-IgE mechanisms. The likelihood of breakthrough reactions (BTR) during desensitization is low and, most are mild; in fact moderate to severe reactions are infrequent.

In this document, sixteen Allergy Departments belonging to the ARADyAL Spanish research network present a review of the available scientific evidence and provide general guidelines for the diagnosis and management of DHR to ChD and mAb, focusing on the desensitization procedure.

Resumen

La desensibilización a medicamentos ha permitido la administración de fármacos de primera línea en pacientes con reacciones de hipersensibilidad (RH) a quimioterápicos (QT), incluyendo los anticuerpos monoclonales (AcM). La desensibilización es un procedimiento seguro y altamente efectivo, no únicamente para las reacciones mediadas por IgE sino también para aquellas relacionadas con un mecanismo independiente de IgE. El riesgo de reacciones durante la desensibilización es bajo y frecuentemente las reacciones observadas son leves, considerándose infrecuentes las reacciones moderadas o graves.

En este documento, dieciséis Servicio de Alergia pertenecientes a la red española de investigación ARADyAL presentan una revisión de la evidencia científica disponible y sugieren unas pautas de actuación generales para el diagnóstico y manejo de las RH a QT y AcM, centrándose en el proceso de desensibilización.

INTRODUCTION

Over the past 15 years, rapid drug desensitization (RDD) has allowed first line therapies in patients with drug hypersensitivity reactions (DHR) to chemotherapeutic drugs (ChD) including monoclonal antibodies (mAb) [1]. RDD is a procedure in which an offending drug is administered in gradual increments until the total dose is reached, resulting in a temporary immune tolerance [2–4]. This is crucial in patients with malignancies, hematological and chronic inflammatory diseases when no comparable alternative is available.

Desensitization is a safe and highly effective procedure, not only for IgE-mediated reactions but also for those mediated by non-IgE mechanisms [3,5]. The benefits of the procedure include an improvement in the overall survival of treated patients compared to using no-first line treatments [5–7], as well as a reduction in costs [5]. The likelihood of breakthrough reactions (BTR) during desensitization is low and, moderate to severe reactions are infrequent [8]. The appearance of BTR can guide amendments in the following protocols and include changes in the number of bags, premedication, anticipatory medication between steps, administration of intravenous fluids, and the addition of intermediate steps [8].

Sixteen Allergy Departments belonging to the ARADyAL Spanish research network [9] recently demonstrated that there is a considerable variation in the allergological study across Spain of both ChD and mAb, especially in diagnostic procedures and therapeutic approaches, including desensitization with its indications, contraindications and management of BTR [10]. In this document, we present a review of the available scientific evidence and provide general guidelines for the diagnosis and management of DHR to ChD and mAb, focusing on the desensitization procedure.
CANCER CHEMOTHERAPY AND HYPERSENSITIVITY REACTIONS

CLASSIFICATIONS AND MECHANISMS

According to the onset of symptoms during DHRs, these are classified as immediate (IDHR) or non-immediate (NIDHR). The former typically occur within the first 1-6 hours after the administration of a treatment, whereas NIDHRs usually occur days or weeks after it [11].

Phenotypes are defined by clinical presentation, and endotypes refer to the cellular and molecular mechanisms of the DHRs [12]. The phenotypes described in IDHRs to ChD and mAb include: type I reactions, cytokine release reactions (CRR), mixed and indeterminate reactions (Figure 1) [13,14]. Type I reactions encompass mast cell (MC)/basophil activation that will lead to the release of mediators through IgE and non-IgE mechanisms including: activation of the FcεRI and FcγRIIA by by IgE and IgG respectively, direct activation of MCs by the C3a and C5a complement fractions and through the MRGPRX2 receptor. In the cytokine release endotype, the increase in cytokines as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6, can be originated from multiple cellular sources, including T cells, monocytes, and macrophages [8,15] (Figure 1).

NIDHR have been less studied, phenotypically they may range from non-severe maculopapular exanthema (MPE) to severe reactions (eg, Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN]). The related endotypes include immune complexes deposited in tissues that may cause injury either locally or systemically, as described with infliximab, etanercept, and adalimumab [14], and also T-cell activation, as described with temozolomide, rituximab, infliximab and taxanes among others [16–18]. Recently, the "converter phenotype" was described in patients treated with taxanes...
who present NIDHRs and in subsequent exposures develop IDHRs, generally type I reactions[19].

SEVERITY CLASSIFICATION

Different schemas for organizing DHR severity have been proposed, the most straightforward because is quick and easy to apply, is that proposed by Brown (Table 1) [20]. Recently, Madrigal-Burgaleta et al [21], published a new more extensive and detailed classification, known as “Ramon y Cajal University Hospital (RCUH) classification for DHR” (Table 2). Both of them are useful, although RCUH includes a broader spectrum of symptoms related to different DHR phenotypes and also the time of onset of the reaction as a severity variable.

BOX 1. Practical recommendations

- DHRs are classified as immediate or non-immediate considering whether they occur within or after the first hour of exposure to the drug.
- Phenotypes and endotypes based on precision medicine are needed to address the diagnosis and the management of DHR focusing on desensitization.
- Classification of severity is important to stratify the risk of patients, approach the allergology work up and guide the therapeutic management.

HYPERSENSITIVITY TO CANCER CHEMOTHERAPY

Any antineoplastic agent could potentially induce DHR. The agents most frequently involved include the following:
1. CHEMOTHERAPEUTIC AGENTS

PLATINUM SALTS

DHRs to platinum compounds are most often IgE-mediated, although non-IgE mediated or mixed reactions have also been reported[22,23]. Its incidence is directly related to the number of exposures [24]; less than 1% in patients who have received ≤5 carboplatin cycles and up to 46% in those with at least 15 cycles suffers a reaction [25,26]. Similarly, the incidence of oxaliplatin reactions range from 7.1% in the first six cycles to 20.6% when patients receive more than six cycles, with the majority reacting during the 7th to 9th infusion [27]. However, patients who develop CRR with oxaliplatin usually react during the first exposures [13]. Similar findings are obtained with cisplatin whose incidence varies from 5% to 20% [28]. Other risk factors for DHRs to carboplatin include a previous history of drug allergy, a prolonged platin-free interval, high doses of carboplatin [24,29] and carrying BRCA1/2 mutations [30].

NIDHRs are uncommon and mostly mild, highlighting the MPE [31]. In addition some cases of antibody-mediated thrombocytopenia, delayed vasculitic urticaria [28,32], and pulmonary fibrosis have been reported [33].

Finally, cross-reactivity between carboplatin and oxaliplatin has been estimated to be between 37-45%, being much lower with cisplatin [34].

TAXANES

Taxanes were originally transformed, through a semisynthetic process, from different parts of the European yew tree, Taxusbaccata. Currently the estimated incidence of IDHR to paclitaxel is 10%, around 5% to docetaxel and cabazitaxel and less than 4% to nab-paclitaxel [35]. Symptoms mainly occur during the first cycle, within minutes of
starting the infusion [36]. It is not clear if the taxanes themselves or the vehicles in which they are dissolved are responsible for the majority of the reactions [37]. Cross-reactivity between paclitaxel and docetaxel has been reported to be up to 50% [31]. Despite the fact that nab-paclitaxel has been tolerated in many patients with severe DHRs to paclitaxel or docetaxel [38–40], there are reports of patients who have also reacted to nab-paclitaxel after having a reaction with paclitaxel [41].

Several cases of life-threatening NIDHRs such SJS and TEN induced by paclitaxel and docetaxel have been reported [42,43].

**OTHER CHEMOTHERAPEUTIC DRUGS**

Doxorubicin is an anthracycline topoisomerase inhibitor. The incidence of IDHRs is 0.6–3% with doxorubicin and 9% with liposomal doxorubicin [44]. Clinical reactions occur during the first minutes of the infusion in the first or second cycle and the increased frequency of reactions with liposomal doxorubicin is thought to be attributed to complement activation by liposomes [45]. Premedication and slowing the infusion rate have reduced the frequency of reactions to less than 1% [46].

Despite their frequent use, other ChDs such as cyclophosphamide, gemcitabine, irinotecan, or fluorouracil are rarely involved in DHRs; we offer extended information about these in Table 3.

2. **MONOCLONAL ANTIBODIES**

The degree of humanization and other factors related to the mAbs or the treated disease may affect the immunogenicity risk of a biological drug [47]. Even fully human proteins can elicit an immune response, producing anti-drug antibodies (ADA) and DHRs [48]. Regarding ADAs, they not only may shorten drug half-life but also mediate
mild to serious DHRs [47,48]. For this reason, DHRs are common, especially with some biologics such as rituximab or trastuzumab [18,49].

mAb reactions are usually phenotype I, and a change to the CRR phenotype may occur during desensitization treatment, although it is not entirely clear why, it is possible that standard premedication may block MC activation but not symptoms induced by cytokines [14].

RITUXIMAB

Rituximab is a chimeric murine/human IgG1 kappa mAb directed against CD20. It is indicated for the treatment of patients with Non-Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) [50]. Rituximab administration is commonly associated with CRRs that usually occur during the first infusion, but can also induce IgE-mediated reactions [14,51,52]. In addition, some cases of TEN, SJS and serum sickness disease (SSD) have been reported [53,54].

CETUXIMAB

Cetuximab is a chimeric mouse/human IgG1 mAb against the epidermal growth factor receptor (EGFR). It is used for the treatment of head and neck and colorectal cancer [55]. The incidence of IDHRs in Cetuximab is estimated at 3%. This mAb can induce anaphylaxis during the first exposure due to the presence of preexisting IgE antibodies against galactose-α-1,3-galactose, a oligosaccharide expressed in the Fab portion of cetuximab [55–57].

OTHER MONOCLONAL ANTIBODIES

Given the increasingly widespread use of mAb in the treatment of different neoplastic, autoimmune and inflammatory diseases, others have also been implicated in DHRs and
case reports are becoming more frequent. We offer extended information about these in table 3.

3. PROTEIN KINASE INHIBITORS (PKI)

PKI represents a new approach to cancer treatment with a targeted therapy. The incidence of DHRs to PKIs is unknown and some cases of IDHRs, such as urticaria and angioedema [58–61], as well as NIDHR, have been reported. The most frequent NIDHR are MPE and non-immediate urticaria [62–64], although some cases of SJS induced by regorafenib (inhibitor of vascular endothelial growth factor receptor [VEGFR]), ribociclib and palbociclib (inhibitors of cyclin-dependent protein kinases [DCK]) have been described [65,66].

Cross-reactivity between PKIs have been suggested between dafrafenib and vemurafenib, as both are target B-Raf inhibitors and have similar chemical structure [67].

ALLERGOLOGICAL STUDY

1. SKIN TESTS (ST)

Skin prick test (SPT) withChD and mAbs should be done at full strength of the drug, followed if negative, by intradermal test (IDT) using serial dilutions (Table 4). Results would be interpreted at 15-20 minutes, and after 24 and 72 hours if a NIDHR is suspected [68]. Although the published information is scarce, it seems that patch tests are not effective in the study of reactions to these drugs [69].

As with other DHRs, the time interval between the initial reaction and ST can affect the results, therefore, it is recommended to perform them at least 4 to 6 weeks after and within 6 months of the reaction, to avoid false negative results [70,71]. When using
dilutions of uncertain significance, it is advisable, when possible and considering the drug tested, to use negative controls [72].

**Platins:** ST with oxaliplatin have high positive predictive value (VPP) and low negative predictive value (NPV): 92% (95%CI, 81.4-102.6) and 56.4% (95%CI, 40.8-72.0) respectively [73].

In order to prevent reactions, some authors recommend performing routinely ST to platins after the sixth cycle in patients on the first line of treatment, or after the second cycle in those patients on the second line of treatment, especially if there was a treatment-free period. In case of positive ST, the platinum involved should be reintroduced with a desensitization protocol [3,74,75]. It should be noted that IDHR reactions may also occur in patients with positive delayed ST [76].

**Taxanes:** Both, NPV and PPV are unknown. Positive results in ST with these drugs varies according to the geographical area studied, and some authors have suggested that some patients may be sensitized to yew tree, an environmental allergen, and due to cross-reactivity, would present IgE-mediated IDHR when being exposed even for the first time to these drugs [77,78].

**Drugs not to be used in skin tests:** Some antineoplastic agents, such as anthracyclines, vinblastine, vincristine, mitomycin C and mechloretamine are vesicants, and STs should not be performed [72].

The concentrations most used to perform ST with ChDs and mAbs, which have been shown to be non-irritating, are shown in Table 4.
2. IN VITRO TESTS

BIOMARKERS

Tryptase

Tryptase levels increase from 15 minutes to 3 hours, with a peak about 120 minutes after reaction onset [79,80]. The main limitation of this test is that according to some publications, up to 40% of patients do not show a significant increase during anaphylaxis. In this context, serial tryptase determination have shown to increase its sensitivity as a biomarker [80] and applying the the formula (baseline x 1.2)+2, especially if basal tryptase levels are low, allows identifying patients with MC release even if the limit of 11.4 ng/ml is not exceeded [81–83]. In patients with a baseline tryptase >7.5 ng/ml, tryptase genotyping should be considered. An increased alfa-tryptase genes copy number have been observed in a recently described syndrome called Hereditary Alpha Tryptasemia, that has also being linked to a higher risk for hypersensitivity reactions [84–86].

Cytokines

The cytokines released during DHRs come mainly from lymphocytes and macrophages. Cytokines maximum levels are found around 100 minutes after the reaction onset and sustained for as long as 10 hours [82]. IL-6 is proposed as a biomarker of CRR [14,87].

Total IgE and Specific IgE

Total IgE has been suggested as a good predictor of a positive hypersensitivity diagnosis for platins [88], although further research is required.

DHR diagnosis to platinum compounds has been studied in large samples of patients, allowing to establish the specific IgE (sIgE) diagnostic yield to these agents, showing...
high specificity (75-100%), but low sensitivity (34-75%) [22,23,73,89,90]. On the other hand, sIgE to taxanes has been detected only in one patient [91].

Basophil activation test (BAT)

Several studies have evaluated the value of BAT in the diagnosis of DHRs to platins [23,71,92,93]. Recently, Giavina-Bianchi P et al. [23] estimated that BAT has a sensitivity of 73% and a specificity of 100% for platinum agent DHRs. In addition, they observed higher CD63 expression in patients with severe BTR during desensitization. BAT could be used as a risk biomarker prior desensitization, although further studies are required to validate this technique.

**In vitro** diagnostic tests for DHRs to mAbs are mostly not standardized and have been performed in some cases report [94]. Regarding the BAT with these drugs, more studies with a large sample of patients are needed to establish its usefulness as a diagnostic tool.

3. DRUG PROVOCATION TEST

Drug provocation test (DPT) is the controlled administration of a drug and it is considered the gold standard to establish or exclude the diagnosis of hypersensitivity [95–97]. DPT should only be performed under the most rigorous surveillance conditions and taking the same precautions and considering the same contraindications established for other drugs by the international guidelines [95–98].

DPT prior to desensitization has scarcely been used as a diagnostic tool in DHRs to ChDs and mAbs[21,70,73,78,90]. In the largest reported series, 341 DPTs were performed in patients with mild or moderate DHRs and negative ST [21]. The authors reported 67% negative DPT, corresponding to 44% of all referred patients; 69% were taxanes, 46% platins and 78% biological agents. Indeed, only fifteen percent of the
positive DPT showed a severe reaction. These results suggest that performing DPT prior desensitization may exclude hypersensitivity in some cases and avoid unnecessary desensitization.

The methodology for DPT with ChDs and mAbs reported by Madrigal-Burgaleta et al. [21,73,90] implies the administration of the culprit drug according to manufacturer’s instructions and institutional protocols [95–97], including standard premedication and additional required medications (other antineoplastics, leucovorin, etc.). Indeed, beta-adrenergic blocking medications must be held for 24 hours before the DPT. Patient’s scheduled treatment is used to perform the DPT to avoid delays or overdose. In case of a positive DPT, the infusion should be held and the DHR treated according to the severity [20,21]. Once symptoms are resolved, usually within 30 minutes, the infusion can be restarted at 1/4 of the final infusion rate for 15 min, and then increased to 1/2 until all the medication is administered (“restart protocol”). All patients with a negative DPT must be closely supervised during subsequent standard drug administrations.

DPTs with other drugs such as premedications, concomitant drugs, additional ChDs or mAbs possibly involved in the initial reactions is recommended to be performed before DPT with the culprit drug [21,73,90,99].

Castells et al [70] also reported a progressive approach to taxanes reintroduction in 49 patients with negative ST and grade 1-2 IDHR and mild NIDHR. The protocol included premedication with montelukast, ASA and/or zileuton. The infusion started at 10 ml/h and progressively increased to 160 ml/h, using 10-fold increments between steps, and a final infusion rate equivalent to a regular infusion [70]. All procedures were performed in the desensitization unit with 1:1 nursing: patient. Only 3 patients had a reaction, two (4%) grade 1 and 1 (2%) mild delayed reaction.
Recently, Martí-Garrido et al. published tolerance to ChDs and mAbs during DPT in 22/23 patients with mild reactions and negative ST, disregarding the need for desensitization in 24% of their patients [100].

Finally, in a recent multicenter study by the European Network of Drug Allergy (ENDA) [78], 16 patients with grade 1 reaction to paclitaxel or docetaxel and negative ST underwent a DPT. The culprit drug was administered at 10 ml/h for the first hour and the rest according to manufacturer instructions. DPT was well tolerated in all patients.

Box 2. Practical recommendations

- ST are useful to identify immediate, probably IgE-mediated reactions, but also non-immediate reactions when delayed lecture is performed. Patch tests have not demonstrated their efficacy in the study of NIDHR to these drugs.
- Serum tryptase is the best available biomarker for identifying anaphylactic reactions.
- IL-6 seems to be a good biomarker in CRR.
- DPT is the gold standard to confirm or exclude DHRs to ChDs and mAbs. Performing prior to desensitization optimizes patient management, since may avoid unnecessary desensitization.
- DPT is a high risk procedure that requires proper patient selection, an experienced allergist, and a proper setting ready to treat possible reactions during the procedure.
DRUG DESENSITIZATION

1. BIOLOGICAL PRINCIPLES OF DESENSITIZATION

*In vitro* models of rapid IgE desensitization show that sensitized MCs became unresponsive to the allergen by (1) starting with subthreshold dose of antigen (1/1000 or 1/100), (2) increasing doses at fixed time intervals and (3) increasing the dose 1.5-2.5 times at every step[4,101,102]. Desensitized MC demonstrated almost complete inhibition of β-hexosaminidase immediate release, early and late TNF-α release, IL-6 production, *de novo* synthesis of lipid mediators, calcium influx, and arachidonic acid metabolism activation[102–104], meaning the inhibition of both the early and late MC responses. Additionally, desensitization impairs the internalization of the antigen/IgE/FcεRI complexes[103,105]and induces the decrease of some signal transducing molecules such as Syk[106,107]. Recently, it was hypothesized that multiple suboptimal antigen doses during desensitization might result in recruitment of the inositol phosphatase SHIP-1 into the plasma membrane, that may tip the balance between positive and negative signaling pathways that regulate degranulation [108].

Rapid IgE desensitization is antigen specific meaning that the activating signal transduction pathways are intact for a second allergen. In humans, temporary immune-tolerance is achieved in hours and can be maintained if drug antigens are administered at regular intervals, being reversible over 2–3 days, depending on pharmacokinetic parameters[106]. Successful desensitization has been related to the increase of IL-10 [109]. The mechanism of rapid desensitization to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is thought to be different from ChDs and mAb and based on a decreased production of leukotrienes and tryptase [110].
2. PATIENT’S SELECTION

Rapid Drug Desensitization (RDD) can be performed in patients of any age and also in pregnant women [11] and even in patients with mastocytosis [111,112], and should be considered standard of care when patients need first line therapy [113]. It has been successfully used in patients with different phenotypes of IDHRs, and in NIDHRs is restricted to MPE or fixed drug eruption (FDE) [11,98].

The algorithm for conducting drug desensitization is shown in Figure 2.

3. RISK STRATIFICATION

Mild symptoms and negative STs are associated with lower risk of reaction, while moderate to severe symptoms and/or positive skin or serological tests indicate higher risk [3,4,23,70]. Another factors such as comorbidities (eg, heart diseases or severe respiratory failure), use of concomitant medications that may interfere with the treatment of a possible reaction, such as beta blockers must be considered when risk stratification [2].

Using the RCUH classification for DHRs to ChD and mAbs [21] (Table 2) and the presence of patients and/or hospital-related factors (Table 5), we propose a risk stratification for RDD (Table 6) and its management (Table 7).

4. RDD PROTOCOLS: EFFICACY AND SAFETY

IMMEDIATE REACTIONS

Several intravenous and subcutaneous desensitization protocols for IDHR to ChD and mAbs have been reported [5,14,52,70,90,114–119]. The Brigham and Women’s Hospital group (BWH) has reported the largest worldwide series of 2177 RDD with ChD and mAbs using rapid multisolution and multistep protocols administered over 5.7
This is a 3-bags/12-steps protocol based on an in vitro mouse bone marrow-derived MC model [102,103], with and starting concentration dose of 1/100, with a fold increase of 2 to 2.5 in each step and a time interval of 15 minutes between them. This is a flexible protocol that must be individualized in each patient according to risk stratification, and can be lengthened (4-bag/16-steps) in high-risk patients, or shortened (2-bag/8-steps, 1-bag/4-steps) depending on tolerance and the initially estimated risk [14,70]. Indeed, this protocol allows the final rate in case of no BTR [4,5].

Based on the BWH protocol, several others have been published using different dilutions, fold increments and premedication, sharing all of them a high degree of success and a low rate of BTR (see Table 8).

Madrigal-Burgaleta et al. published a 3-bag/10-steps protocol for the first time in 2013 [90] and a large series of 1050 desensitizations in 2019 [21]. This protocol uses ‘flushing steps’, meaning that the infusion line is primed with diluent instead of the antineoplastic agent.

Some authors have used a 1-bag protocol (undiluted solution) to ensure dilution stability. Perez-Rodriguez et al. demonstrated its safety in 490 desensitizations with different ChD and mAb[121]. In this protocol, the infusion rate began at 5 ml/h with increases every 15 minutes up to 125- 250 ml/h, that was the maximum infusion manufacturer/oncologist recommended rate.

Multiple protocols have been reported as single cases with few number of desensitizations for several ChD and mAb such as brentuximabvedotin[122,123], nivolumab[124], alemtuzumab[125,126], atezolizumab[127], bevacizumab [127,128], denosumab[129], daratumumab[130] and canakinumab[131]. Although this is not the
scope of this article, considering the potential utility for the reader and the off-label use of some mAbs, a recent review of desensitization procedures performed with mAbs used in rheumatology has been reported [132].

NON-IMMEDIATE REACTIONS

The EAACI position paper on desensitization in NIDHRs for any drug [133] included among the criteria for desensitization that (1) drug therapy is essential/irreplaceable and more effective than alternatives, (2) unavailability of alternatives, (3) previous reaction is well documented and not severe, eg, MPE or FDE, and (4) the potential benefits outweigh the potential risks. However, these general recommendations are based in short series, due to the lack of controlled studies/consensus on protocols, limitation that is even more evident for ChD and mAb.

Sloane et al. [5] published the largest series of RDD performed in 112 patients with mild NIDHRs. Those were performed with high success, following the same 3-bag/12-steps protocol used in IDHRs. These protocols have also been used successfully in a patient with MPE by bendamustine, who had positive skin tests on delay lecture [134].

Interestingly, NIHSRs are observed mostly with taxanes and can shift to immediate reactions upon re-exposure, in a previously mentioned converter phenotype; desensitization can prevent this change [28,70,135]. Picard et al. [70] observed that 20% of patients with NIHSR with taxanes had an IHSR after a new exposure; flushing with onset of ≤48 hours after infusion increased the risk for a BTR (both immediate or delayed) upon a new exposure. These same authors found that patients with mild NIHSR were more likely to resume regular infusions, particularly those with negative ST. However, some of them experienced an IHSR after tolerating 3 regular infusions, and on re-evaluation, showed positive ST.
Other desensitization protocols using different administration routes have been published. Oral desensitization with temozolomide and capecitabine have been successfully performed in a limited series of procedures with delayed MPE [16,136], either using a 1-day/3-concentrations/13-steps protocol, doubling doses every 30 minutes or 3-concentrations/14-steps for temozolomide, or with gradual dose increases in a 16-day protocol in the case of capecitabine.

Desensitization appears to be a safety and efficacy option for treatment of DHR to some PKI (imatinib, crizotinib, sunitinib, sorafenib, alectinib, regorafenib and dabrafenib) [58,61–64,67,137].

5. OPTIMIZING DESENSITIZATION

IDENTIFY RISK FACTORS FOR BREAKTHROUGH REACTIONS

A common finding in the RDD to ChD and mAb series is the high success rate and both the low number and severity of BTR [5,14,21,70,88,121,138]. However, despite being generally mild, there is still up to 25% of reactions [5,14,21,70,88,121,138]. Different risk factors have been described that partially differ from one series to another, as discussed below.

Sloane et al. [5] using a 3-bag/12-steps protocol observed only 26% of BTR during 2177 RDD, mostly mild, immediate, and generally between step 7-12. Most patients (60%) had no reactions during the first RDD, regardless of the initial DHR severity. Actually, a patient with an initial grade 3 reaction had an 86% chance of having a grade 1 or no reaction during the first RDD, and only a 9% of having another grade 3 reaction.

Madrigal-Burgaleta et al. [21] using a 3-bag/10-steps protocol observed 12% of BTR in 1027 RDDs, mostly grade 1 with skin symptoms as a prevailing manifestation. The
associated risk factors were positive ST and atopy (RRR 4.01 [1.8-10.3] and 2.16 [1.6-14.1], respectively). These authors suggested, based on the BTR during RDD, classifying patients into 3 groups: (1)-first RDD reactors, usually with moderate to severe BTR, (2)-reactors after several uneventful RDD, related with no premedication intake, sensitization to new drugs o transition to shorter RDD protocols, and (3)-BTR manifested as fever/chills, that may be the prelude of an anaphylaxis.

Isabwe et al. [14] in a series of 104 RDD to mAbs using a 3-bag/12-steps protocol found, as previously observed, 23% of BTR, mainly grade 1 and mostly during the final step. They observed that positive ST was associated with type I reactions during RDD. Indeed, subsequent procedures decreased the risk of BTR, reaching a plateau after 20 RDD. In fact, grade 2 reactions decreased from 25% to 3% when comparing the first 5 with more than 10 RDD.

Picard et al. [70] in a series of 138 RDD using a 3-bag/12-steps protocol with taxanes observed 21% BTR. Although several factors were evaluated, such as age, cancer type, severity of the initial reaction and ST, only atopy was significantly associated (OR 4.9 [2-22.8]).

Kang et al. [138] in a series of 234 RDD with several ChDs and mAbs using the 3-bag/12-steps protocol found, conversely to other series, that BTR development was associated with the severity of the initial reaction and the administration of previous cycles of the same drug. Indeed, the severity of these BTR was related with these two factors and also with a positive history of drug allergy. Atopy was not considered in the analysis.

Finally, Caiado et al. [88] found that total IgE>100 kU/L and >10 previous cycles were risk factors (OR 8.24 and 4.11, respectively) for BTR, particularly for platinum
compounds. However, atopy, ST results or severity of the initial DHR were not included in the multivariate analysis.

**USING MEDICATION TO REDUCE RISKS: PREMEDICATION**

Additional premedication is often used prior to RDD to avoid DHRs, although the evidence supporting or contraindicating its use is limited.

Most publications based on the BWH protocol [5], show the routinely use of H1-blockers (H1b) and H2-blockers (H2b) in all patients [3,5,14,88,139]. Additional premedication could be administered based on the symptoms that the patient experienced during the initial reaction [140] such benzodiazepines for anxiety [21,88], paracetamol, opioids and other NSAIDs for fever, pain, rigor and chills. Indeed, aspirin and montelukast 10 mg 2 days prior to the desensitization is respectively added in those patients with flushing and respiratory symptoms [5,21,88,140]. Breslow et al [141] demonstrated that those additional drugs, added to the H1b/H2b, successfully reduced the severity of the reactions occurring during desensitization more effectively than a group receiving methylprednisolone (0.5 vs 1.75).

Fluids, normal saline (NS) have also been used as an additional premedication, mostly in CRRs. Isabwe et al [14] showed in 81 RDD that using NS in the routine scheme reduced the severity of the BTR. Similarly, using fluids after a BTR during desensitization, reduced the severity of new DHRs in the subsequent RDD (from 1.3 to 0.35). These authors recommended, for CRR, using 100 ml/h of NS between step 1-11 and increasing to 250 mL/h during step 12.

However, other groups have shown that additional premedication during RDD in taxanes may not be necessary. Lopez-Gonzalez et al [142] did not observe differences in
the frequency/severity of BTR when comparing RDD to paclitaxel using corticosteroids together with antihistamines as a premedication with RDD without this premedication.

Corticosteroids avoidance, unless required as antiemetic or per oncology protocol, is a common recommendation in most of the publications. As Breslow et al [141] showed, corticosteroids use is less effective than ASA or montelukast to prevent some symptoms during RDD.

HANDLING BREAKTHROUGH REACTIONS DURING RDD

Management of BTR is quite homogenous when comparing different centers and involves acute treatment of the reactions and planning of future RDD. Interestingly, as we commented above, repetitive RDD confers a decreased risk of BTR with a plateau after 20 procedures [14,70].

Immediate breakthrough reactions

Most of the existent bibliography refers to immediate BTR because are the most frequent ones (95%) [5,14]. Reactions usually appear in the last steps; steps 7-12 in the case of ChDs and 12 for mAbs [5]. Those that occur during the first steps, that is at a low dose of the drug, suggests patients with high reactivity.

Treatment options based on DHR severity are shown in the figure 3 [1,3,5,14,28,52,73,120,141].

Once symptoms are resolved, drug infusion can be resumed at the same step and infusion rate when reaction appears [1,3,5,14,28,52,141,143]. Only in case of severe reactions, in agreement with the onco-hematology team, desensitization must be stopped and postponed until further tailored changes in pretreatment scheme and/or the protocol have been made.
After a BTR during a RDD, the premedication and protocol should be reevaluated and customized in base of the severity of the reaction, the step where it occurred, the values of acute phase biomarkers (eg, tryptase, IL-6; if they are available) and the result of a new allergological evaluation. Several recommendations for customizing subsequent RDD are summarized in table 9.

Pretreatment with omalizumab may be considered when the measures previously described fail, although the quality of the evidence is low and many issues concerning optimal dose and pretreatment duration remain unanswered [144]. Some case reports have been published with carboplatin (3 patients) [145,146] and oxaliplatin (5 patients) [21,147–149], with different approaches but common successful outcomes. In most of them 300 mg omalizumab was used, and at least 1 dose was administered before attempting desensitization.

Non-immediate reactions

The EAACI position paper on desensitization in NIDHR [133] states that there are no sufficient data for recommendations on the particular approach of preventing delayed BTR, although antihistamines, corticosteroids and some immunosuppressant have been tested with heterogeneous success. In the current published series of RDD to ChDs and mAbs there is almost no information regarding this issue, and a vague and empirical recommendation of using corticosteroids 2 to 7 days after RDD was made by Sloane et al [5].

BOX3. Practical recommendations

- RDD is an allergen specific procedure meaning that the molecular mechanisms of
MC activation are rendered inactive only to the allergen used for desensitization.

- Risk stratification for new severe reactions must be performed based on the characteristics of the initial reaction and the result of the allergological study.
- IDHRs greatly benefit from RDD; multiple protocols (intravenous, subcutaneous or oral) have proven to be both useful and safe.
- Mild NIDHRs, including MPE, FDE and those with a converter phenotype, can also be desensitized and protocols used in IDHRs can be equally useful and effective.
- Premedication schemes for IDHR are based on the symptoms experienced during the initial reaction. Additional premedication can be added in case of BTR.

**ORGANIZATION IN CLINICAL PRACTICE**

The goal of RDD is to achieve tolerance with the least possible side effects. The process of desensitization must be a comprehensive approach including [2,150,151]:

2. Development of a protocol for the targeted drug and its implementation in appropriate facilities and by trained personnel.
3. Patient information and written consent.
4. The evaluation of the potential BTR (immediate or delayed) and subsequent planning of new tailored RDD when needed.
1. WORK CIRCUIT WITH A MULTIDISCIPLINARY TEAM

There must be a designed coordination protocol with participation of a multidisciplinary team including the medical services referring patients (eg, Oncology, Hematology, Internal Medicine, among others), Pharmacy, Allergy and Nursing units, as well as quality indicators to assess the functioning of the protocol. Among the different roles in these teams, allergists are responsible for assessing the patient with DHR and making the risk stratification, deciding the location of RDD, establishing the protocol and number of steps, overseeing the process from the beginning and are ultimately responsible during drug administration. Nurses trained in allergy are responsible for conducting the ST and DPT, treatment administration, implementing and supervising the RDD protocol. (Figure 4). Patient must be fully informed about the DHR experienced; the allergological study; the therapeutical options; and the RDD process. The patient must give written informed consent along the procedures after all the doubts have been solved. The RDD work circuit and protocol should have received the institutional ethical committee’s approval.

2. SAFETY RECOMMENDATIONS FOR THE DIAGNOSIS AND DESENSITIZATION OF CANCER CHEMOTHERAPY TRAINED STAFF

All staff (physicians and nurses) involved in RDD must be familiar with the management of the drug being administered, the desensitization protocols, the early identification of BTR, including anaphylaxis, the treatment of DHRs including cardiopulmonary resuscitation training and the regulations on handling cytostatic drugs [2,152,153]. The recommendation is having one nurse per patient, especially in those who have had severe reactions [46].
ChDs and mAbs are commonly used in combination regimens. In some situations, the order of administration may increase the cytotoxicity or antagonize the mechanism of the second agent. So it is important to know whether there is a preferred order in drug administration to establish a sequence chart for agents given on the same day [154].

Another important point is to know if the individual infusion line (usually 22 ml length) is previously primed with the ChD or with the diluter substance to schedule or not intermedia steps [90].

SPECIFIC RESOURCES AND ADEQUATE SURVEILLANCE SETTING

RDD must be performed in a setting with resuscitation personnel and resources easily available. Depending on risk stratification and management proposal (Table 7), this setting can be an intensive care unit (ICU), inpatient floor or outpatient allergy/oncology day unit [98]. All the resources to perform a desensitization, such as infusion pumps, heart monitor, hazardous drug waste, recliners or beds must be available [155].

In high risk patients, RDD may be performed in an ICU to minimize risks. Once the patient has completed a successful procedure, RDD can be moved to a day hospital room or outpatient infusion clinic and a modification of the protocol can be considered [3,21,52,70].

3. SAFE HANDLING OF ANTINEOPLASTIC AND BIOLOGIC AGENTS IN ALLERGY UNITS

The antineoplastic and biological agents involved in DHRs are considered hazardous drugs (HD) [156]. Every Allergy Unit must have written specific protocols that include a list of HD used and the appropriate Personal Protective Equipment (PPE) accordingly.
with the diagnostic and therapeutic procedure [90,157]. All staff handling HD must demonstrate proficiency before manipulating them and at least every 12 months thereafter [158]. The recommendations below are based on different guidelines [156,157,159].

PERSONAL PROTECTIVE EQUIPMENT (PPE)

It should include gloves, preferably made from nitrile with standard ASTM D6978, gowns against cytotoxic drugs with greater protection in the area of sleeves and front, safety anti-splash goggles and self-filtering masks (FFP3).

GUARANTEED SAFE WORK PRACTICES AND ACCIDENTAL HAZARDOUS DRUG EXPOSURE ACTION PLAN

ChDs and mAbs require special handling due to the risk of aerosol breathing or drop splashing, and skin contact during diagnostic or therapeutic procedures. The proper and safe use of each element of PPE depends on the procedure performed and is detailed in table 10. ChD handling must be performed in a dedicated workplace, with spill kit and HD waste container readily available. Syringe preparations for ST must have Luer-Lock connections to prevent spills. During DPT or desensitization, it should be recommended the use of closed transfer systems devices (CTS) and preparations with valve systems with the incorporated connector. HD waste (lancets for ST, syringes, drugs bags, tubing, protective equipment) must be placed in a container clearly identified with cytotoxic hazard symbol. A spill kit and written recommended steps for spill cleanup procedure should be readily available within the work areas where ST, DPT and desensitization are performed.
BOX4. Practical recommendations

- A successful RDD requires a multidisciplinary team that includes physicians, pharmacists, nurses, as well as quality indicators to evaluate the functioning of the protocol.

- Allergists are responsible for the allergological study, identification of patients requiring RDD, the preparation of RDD protocols, supervision of the procedures and modification of the protocols in case of BTR.

- RDD must be performed in a suitable facility with all the necessary resources to treat potential complications and with easy access to the ICU.

- The cancer chemotherapy involved in DHRs are considered dangerous drugs. All the staff involved in desensitization must be trained in the use of personal protective equipment to handle them and work in safe areas that have action plans for accidental exposure to these drugs.

KEY MESSAGES

- DHR must be studied by trained allergists who should focus the diagnostic and therapeutic options with a personalized approach in patients with cancer.

- RDD is an effective and safe option which allows patients with DHR to continue first line treatment.

- Multidisciplinary team, facilities and clinical resources should be available prior to performing a RDD.
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MPB has received in the past 36 months, grants from Instituto Carlos III and Fundación Merck Salud.

MFR has received in the past 36 months:

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<th>Spanish Government (ISCIII)</th>
<th>Grants to her institution</th>
</tr>
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</tr>
<tr>
<td></td>
<td>Diater</td>
<td></td>
</tr>
<tr>
<td>Payment or honoraria for lectures,</td>
<td>Aimmune Therapeutics</td>
<td></td>
</tr>
<tr>
<td>presentations, speakers bureaus, manuscript</td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>writing or educational events</td>
<td>SPRIM</td>
<td></td>
</tr>
<tr>
<td>Support for attending meetings and/or travel</td>
<td>Aimmune Therapeutics</td>
<td></td>
</tr>
<tr>
<td>Participation on a Data Safety Monitoring</td>
<td>ALK, Diater, GSK</td>
<td></td>
</tr>
<tr>
<td>Board or Advisory Board</td>
<td>HAL Allergy</td>
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<td>Thermofisher Scientific</td>
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</tr>
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</table>

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107. MacGlashan D, Miura K. Loss of syk kinase during IgE-mediated stimulation of


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TABLES AND FIGURES

Table 1. Brown’s classification of hypersensitivity reactions.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild (skin and subcutaneous tissues only)(^a)</td>
<td>Generalized erythema, urticaria, periorbital edema, or angioedema.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)</td>
<td>Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain.</td>
</tr>
<tr>
<td>3</td>
<td>Severe (hypoxia, hypotension, or neurologic compromise)</td>
<td>Cyanosis or SpO₂ ≤92% at any stage, hypotension (SBP &lt; 90 mm Hg in adults), confusion, collapse, LOC, or incontinence.</td>
</tr>
</tbody>
</table>

Adapted from Brown SGA [20]. Abbreviations: SBP, Systolic blood pressure; SpO₂, oxygen saturation; LOC, loss of consciousness.

\(^a\)Mild reactions can be further subclassified into those with and without angioedema.
Table 2. Ramon y Cajal University Hospital classification for drug hypersensitivity reactions.

<table>
<thead>
<tr>
<th>I. Mild reaction</th>
<th>II. Moderate reaction</th>
<th>III. Severe reaction</th>
<th>IV. Anaphylactic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>-Slow onset (＞15 min):</td>
<td>-Rapid onset (＜15 min)</td>
<td>-Immediate onset (or rapid progression) of any of the latter and manifestation of any of the following:</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Generalized urticaria/angioedema</td>
<td>General urticaria/angioedema</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Local urticaria/angioedema</td>
<td>Coryzal symptoms</td>
<td>Coryzal symptoms</td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Fever/chills (＜38°C)</td>
<td>Irritative cough</td>
<td>Irritative cough</td>
<td>Sense of impending doom</td>
</tr>
<tr>
<td>Mild back pain</td>
<td>Dyspnea (SpO2 ＞ 92%)</td>
<td>-and/or manifestation of</td>
<td>Fainting</td>
</tr>
<tr>
<td></td>
<td>Throat tightness</td>
<td>Throat tightness with dysphagia and/or dysphonia and/or stridor</td>
<td>Loss of sphincters control</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Wheezing</td>
<td>Cardiovascular and/or respiratory arrest</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Chest tightness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe back pain</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever (＞38°C)</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SpO2 ＜ 92%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diaphoresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Madrigal-Burgaleta et al [21].
Table 3. Characteristics of the hypersensitivity reactions to cancer chemotherapy (other than taxanes and platinum compounds).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Type</th>
<th>Indications</th>
<th>DHR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapeutic drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Nitrogen mustard alkylator</td>
<td>Alkylating agent</td>
<td>HL, leukemia, ovarian and breast cancer</td>
<td>Rare IDHR: IgE-mediated (apparently to the active metabolite)</td>
<td>[3,5,148,149]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rare NIDHR: MPE</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Nucleoside metabolic inhibitor</td>
<td>Analog of deoxycytidine</td>
<td>Ovarian, breast, NSLC and pancreatic cancer</td>
<td>Rare IDHR: IgE-mediated</td>
<td>[5,21,150–152]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NIDHR: MPE,TEN, SJS</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Topoisomerase inhibitor</td>
<td>Enzyme inhibitor</td>
<td>Colorectal cancer</td>
<td>Rare IDHR: IgE-mediated</td>
<td>[21,73,153]</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Nucleoside metabolic inhibitor</td>
<td>Antimetabolite</td>
<td>Breast, colorectal, gastric and pancreatic cancer</td>
<td>Rare IDHR: IgE-mediated</td>
<td>[154]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rare NIDHR: MPE</td>
<td></td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>Chimeric</td>
<td>NHL and CLL</td>
<td>IDHR: IgE-mediated and CRR, NIDHR: SSR, TEN, SJS</td>
<td>[14,50–54]</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Chimeric</td>
<td>Head and neck cancer and colorectal cancer</td>
<td>IDHR: IgE-mediated and CRR</td>
<td>[55–57]</td>
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<tr>
<td>Trastuzumab</td>
<td>HER 2</td>
<td>Humanized</td>
<td>Breast cancer, gastric and gastroesophageal cancer</td>
<td>IDHR: IgE-mediated and CRR</td>
<td>[155–157]</td>
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<tr>
<td>Pertuzumab</td>
<td>HER 2</td>
<td>Humanized</td>
<td>Breast cancer</td>
<td>IDHR: IgE-mediated</td>
<td>[158]</td>
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<td>Bevacizumab</td>
<td>VEGF</td>
<td>Humanized</td>
<td>Colorectal cancer</td>
<td>IDHR: IgE-mediated and CRR</td>
<td>[159,160]</td>
</tr>
<tr>
<td>MAb/Target</td>
<td>Type</td>
<td>Source</td>
<td>Conditions</td>
<td>IDHR:</td>
<td>NIDHR:</td>
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<td>------</td>
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<tr>
<td>Brentuximab</td>
<td>CD30</td>
<td>Chimeric</td>
<td>SALCL, HL</td>
<td>IgE-mediated and CRR</td>
<td>MPE</td>
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<td>Nivolumab</td>
<td>PD-1</td>
<td>Human</td>
<td>Melanoma, NSLC, renal cancer, HL, neck and head cancer, HCC</td>
<td>IgE-mediated MPE</td>
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Table 4. Recommended drug concentration used for skin testing to cancer chemotherapy.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Concentration (mg/ml)</th>
<th>SPT</th>
<th>ID 1</th>
<th>ID 2</th>
<th>ID 3</th>
<th>References</th>
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<tr>
<td><strong>Platinums</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cisplatin</td>
<td>1</td>
<td>0.1</td>
<td>1</td>
<td></td>
<td></td>
<td>[3,86]</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
<td>[3,86]</td>
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<tr>
<td>Oxaliplatin</td>
<td>5</td>
<td>0.5</td>
<td>5</td>
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<td>[3,86]</td>
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<td><strong>Taxanes</strong></td>
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<td>Paclitaxel</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>[70,131]</td>
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<tr>
<td>Docetaxel</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td></td>
<td></td>
<td>[70,86]</td>
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<tr>
<td><strong>Other chemothrapeutic agents</strong></td>
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<tr>
<td>Doxorubicin</td>
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<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>[166]</td>
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<tr>
<td>Cyclophosphamide</td>
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<td>1</td>
<td>10</td>
<td></td>
<td></td>
<td>[5,73]</td>
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<tr>
<td>Gemcitabine</td>
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<td>3.8</td>
<td>38</td>
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<td>[73]</td>
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<td>20</td>
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<td></td>
<td>[73]</td>
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<td>Fluorouracil</td>
<td>0.01</td>
<td>0.001</td>
<td>0.01</td>
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<td>[154]</td>
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<tr>
<td><strong>Monoclonal antibodies</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
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<td>1</td>
<td></td>
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<td>[14,52,167]</td>
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<tr>
<td>Cetuximab</td>
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<td>5</td>
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<td>[14,57]</td>
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<td>0.016</td>
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<td>0.025</td>
<td>0.25</td>
<td>2.5</td>
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<td>[90]</td>
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<tr>
<td>Nivolumab</td>
<td>1</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td>[116]</td>
</tr>
</tbody>
</table>

Abbreviations: SPT, skin prick tests; ID, intradermal tests; NR, not recommended.
Table 5. Concomitant conditions to consider in risk stratification for desensitization.

<table>
<thead>
<tr>
<th>Patients conditions</th>
<th>Institutional conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled asthma or lung disease</td>
<td>Nurses</td>
</tr>
<tr>
<td>Acute heart disease</td>
<td>More than 2 patients per nurse</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>No specialty-trained staff</td>
</tr>
<tr>
<td>Unavoidable use of beta-blockers</td>
<td>Allergist</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No access to expert allergists in &lt; 2 min</td>
</tr>
<tr>
<td>Acute infections</td>
<td>Institutional factors</td>
</tr>
<tr>
<td>Critical-ill patient</td>
<td>There are no specific areas to perform this technique</td>
</tr>
<tr>
<td></td>
<td>Difficulties to deal with breakthrough reactions</td>
</tr>
</tbody>
</table>

Abbreviations: min, minutes.

Table 6. Risk stratification proposal.

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Grade II and</td>
<td>Grade III / IV</td>
</tr>
<tr>
<td>No patient or institutional conditions</td>
<td>Grade I and - 1 patient condition or - 1 institutional condition</td>
<td>Grade II and - 1 patient condition or - 1 institutional condition or - Positive results on the allergological study</td>
</tr>
<tr>
<td></td>
<td>Grade I and - Positive results on the allergological study</td>
<td>Grade I and - 1 patient condition and - 1 hospital condition and/or - Positive results on the allergological study</td>
</tr>
</tbody>
</table>

Risk stratification proposal considering the severity of the initial DHR, results of the allergological study and the presence of concomitant conditions. Reaction grade is based on RCUH classification for DHR [21].
### Table 7. Management proposal based on risk stratification.

<table>
<thead>
<tr>
<th></th>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPT or supervised regular administration</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Drug desensitization</td>
<td>Drug desensitization</td>
<td></td>
</tr>
<tr>
<td>Recommended setting: ADCU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting dose: 1/100</td>
<td></td>
<td>Starting dose: 1/10000-1000</td>
<td></td>
</tr>
<tr>
<td>Nº of steps: 8-12</td>
<td></td>
<td>Nº of steps: 12-16</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DPT, drug provocation test; ADCU, allergy day care unit; ICU, intensive care unit.

<sup>a</sup>In the DPT, increasing doses of the medication are given until reaching a cumulative dose equal to the usual one, while the supervised regular administration is to repeat the administration of the drug as is normally done under medical supervision.

<sup>b</sup>Some medium risk patients with negative results on the allergological study can be treated as low risk, after a personalized evaluation.

<sup>c</sup>The choice of the desensitization site will depend on the number of patients and the institutional conditions in each case.
Table 8. Desensitization protocols.

<table>
<thead>
<tr>
<th># Bag</th>
<th>Steps</th>
<th>Duration (hours)</th>
<th>RDD reported</th>
<th>Increment dose (fold)</th>
<th>Dose Interval (min)</th>
<th>BTR% (severe%) a</th>
<th>Additional pre-medication</th>
<th>Drugs</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>12</td>
<td>5.7</td>
<td>2177</td>
<td>2-2.5</td>
<td>15</td>
<td>26 (15)</td>
<td>H1b, H2b, ASA, Mtk</td>
<td>Taxanes, Platinum, mAb</td>
<td>[5]</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>5.7</td>
<td>1471</td>
<td>2-2.5</td>
<td>15</td>
<td>9.6 (5.7)</td>
<td>H1b, H2b</td>
<td>Taxanes, Platinum, mAb</td>
<td>[84]</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>4.25</td>
<td>1050</td>
<td>2-2.5</td>
<td>15</td>
<td>12 (10)</td>
<td>ASA, Mtk</td>
<td>Taxanes, Platinum, mAb</td>
<td>[21]</td>
</tr>
<tr>
<td>1</td>
<td>6-9</td>
<td>3.5</td>
<td>490</td>
<td>1.5-2</td>
<td>15</td>
<td>5.3 (12)</td>
<td>H1b, H2b, ASA, Mtk</td>
<td>Taxanes, Platinum, mAb</td>
<td>[113]</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>3.4</td>
<td>211</td>
<td>2</td>
<td>15</td>
<td>16.1 (2.6)</td>
<td>H1b, H2b, Mtk</td>
<td>Paclitaxel</td>
<td>[168]</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>6.3</td>
<td>77</td>
<td>2</td>
<td>30</td>
<td>33 (0)</td>
<td>ASA, Mtk</td>
<td>Cetuximab</td>
<td>[21]</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>4.5</td>
<td>58</td>
<td>4.5</td>
<td>15 (30 min step 15 &amp; 16)</td>
<td>1.7 (0)</td>
<td>H1b, ASA, Mtk, C</td>
<td>Carboplatin, Taxanes</td>
<td>[109]</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2-5</td>
<td>39</td>
<td>10</td>
<td>15</td>
<td>5 (100)</td>
<td>H1b, C</td>
<td>Taxanes, Platinum</td>
<td>[111]</td>
</tr>
</tbody>
</table>

Abbreviations: RDD, rapid drug desensitizations; min, minutes; BTR, breakthrough reactions; Ref, references; H1b, h1 blockers; H2b, h2 blockers; ASA, acetyl salicylic acid; Mtk, Montelukast; C, corticosteroids

a The information in brackets expresses the percentage of severe reactions out of total reactions.
**Table 9.** Potential modification of desensitization protocols after breakthrough reactions.

<table>
<thead>
<tr>
<th>Possible modifications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>New premedication based on BTR symptoms before the infusion or before the step where</td>
<td>[1, 3, 14, 84, 129, 130]</td>
</tr>
<tr>
<td>the reaction occurred</td>
<td></td>
</tr>
<tr>
<td>Change from 3-bag/12-steps to 4-bag/16-steps protocol in case of grade 3 reaction</td>
<td>[13, 14]</td>
</tr>
<tr>
<td>NS as premedication, particularly in CRR</td>
<td>[13, 14]</td>
</tr>
<tr>
<td>Temporary dose reduction</td>
<td>[13, 14]</td>
</tr>
<tr>
<td>Adding intermediate steps</td>
<td>[1, 3, 84]</td>
</tr>
<tr>
<td>Lengthening final step</td>
<td>[13, 14, 84]</td>
</tr>
<tr>
<td>Premedication with omalizumab</td>
<td>[133, 135, 169]</td>
</tr>
</tbody>
</table>

Abbreviations: BTR, breakthrough reactions; NS, normal saline; CRR, cytokine release reaction.
Table 10. Personal protective equipment according to the procedure.

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gloves</td>
</tr>
<tr>
<td>Skin test</td>
<td>Yes</td>
</tr>
<tr>
<td>Intravenous administration with CTS</td>
<td>Yes</td>
</tr>
<tr>
<td>Intravenous administration without CTS</td>
<td>Yes</td>
</tr>
<tr>
<td>Intramuscular administration</td>
<td>Yes</td>
</tr>
<tr>
<td>Subcutaneous administration</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral administration (Tablets)</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral administration (Suspension)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from Power LA et al [145]. Abbreviations: PPE, personal protective equipment; CTS, closed transfer systems device.
**Figure 1.** Phenotypes and endotypes to chemotherapeutic drugs and monoclonal antibodies.

Phenotype I includes symptoms of mast cell activation and *common symptoms* to other phenotypes. CRR phenotype embraces characteristic symptoms of CRR and *common symptoms*. The mixed phenotype there is a mixture of the above, and in the indeterminate phenotype there are only common symptoms.

**Figure 2.** Algorithm for conducting drug desensitization.

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Adapted from Cernadas JR et al [2].

Figure 3. Management of reactions occurring during desensitization (breakthrough reactions).
RDD indicates rapid drug desensitization; min, minutes; H1b, h1 blockers; C, corticosteroids; NSAIDs, non-steroidal anti-inflammatory drugs; NS, normal saline.

*Includes anaphylaxis and anaphylactic shock.

Figure 4. Drug hypersensitivity reaction’s evaluation and desensitization circuit.
DHR indicates drug hypersensitivity reactions; RDD, rapid drug desensitization; ChD, chemotherapeutic drug; mAb, monoclonal antibody.