GUIDELINES

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

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Abstract

Rapid drug desensitization has enabled first-line therapies in patients with drug hypersensitivity reactions to chemotherapeutic drugs including monoclonal antibodies. 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 during desensitization is low, and most are mild; in fact, moderate-to-severe reactions are infrequent.

In this document, 16 allergy departments belonging to the Spanish research network ARADyAL present a review of the available scientific evidence and provide general guidelines for the diagnosis and management of drug hypersensitivity reactions to chemotherapeutic drugs and monoclonal antibodies. Emphasis is placed on the desensitization procedure.

Key words: Drug allergy. Drug hypersensitivity. Desensitization. Chemotherapy. Drug challenge. Monoclonal antibodies.

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 Servicios 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.

Palabras clave: Alergia a medicamentos. Hipersensibilidad a medicamentos. Desensibilización. Quimioterápicos. Prueba de provocación con medicamentos. Anticuerpos monoclonales.

1. Introduction

Over the past 15 years, rapid drug desensitization (RDD) has enabled first-line therapies in patients with drug hypersensitivity reactions (DHRs) to chemotherapeutic drugs including monoclonal antibodies [1]. RDD is a procedure in which an offending drug is administered in gradual increments until the total dose is reached, resulting in temporary immune tolerance [2-4]. This is crucial in patients with malignancies and 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 caused by non–IgE-mediated mechanisms [3,5]. Its benefits include an improvement in the overall survival of treated patients compared with not administering first-line treatments [5-7] and reduction in costs [5]. The likelihood of breakthrough reactions during desensitization is low, and moderate-to-severe reactions are infrequent [8]. The appearance of breakthrough reactions can guide amendments to subsequent protocols. These 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 Spanish research network ARADyAL [9] recently demonstrated that there is a considerable variation in the allergological study of chemotherapeutic drugs and monoclonal antibodies across Spain, especially in diagnostic procedures and therapeutic approaches, including desensitization (with its indications and contraindications) and management of breakthrough reactions [10]. In this document, we present a review of the available scientific evidence and provide general guidelines for the diagnosis and management of DHRs to chemotherapeutic drugs and monoclonal antibodies, with emphasis on the desensitization procedure.

2. Cancer Chemotherapy and Hypersensitivity Reactions

2.1. Classifications and Mechanisms

DHRs are classified as immediate (IDHRs) or nonimmediate (NIDHRs) depending on when symptoms appear. The former typically occur within the first 1-6 hours after the administration of a treatment, whereas NIDHRs usually occur days or weeks later [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 chemotherapeutic drugs and monoclonal antibodies include type 1 reactions, cytokine release reactions, mixed reactions, and indeterminate reactions (Figure 1) [13,14]. Type 1 reactions encompass mast cell/basophil activation that leads to the release of mediators through IgE-mediated and non–IgE-mediated mechanisms including activation of the FcεRI and FcγRIIA receptors by IgE and IgG, respectively, and direct activation of mast cells by the C3a and C5a complement fractions and through the MRGPRX2 receptor. In the cytokine release endotype, the increase in cytokines such as tumor

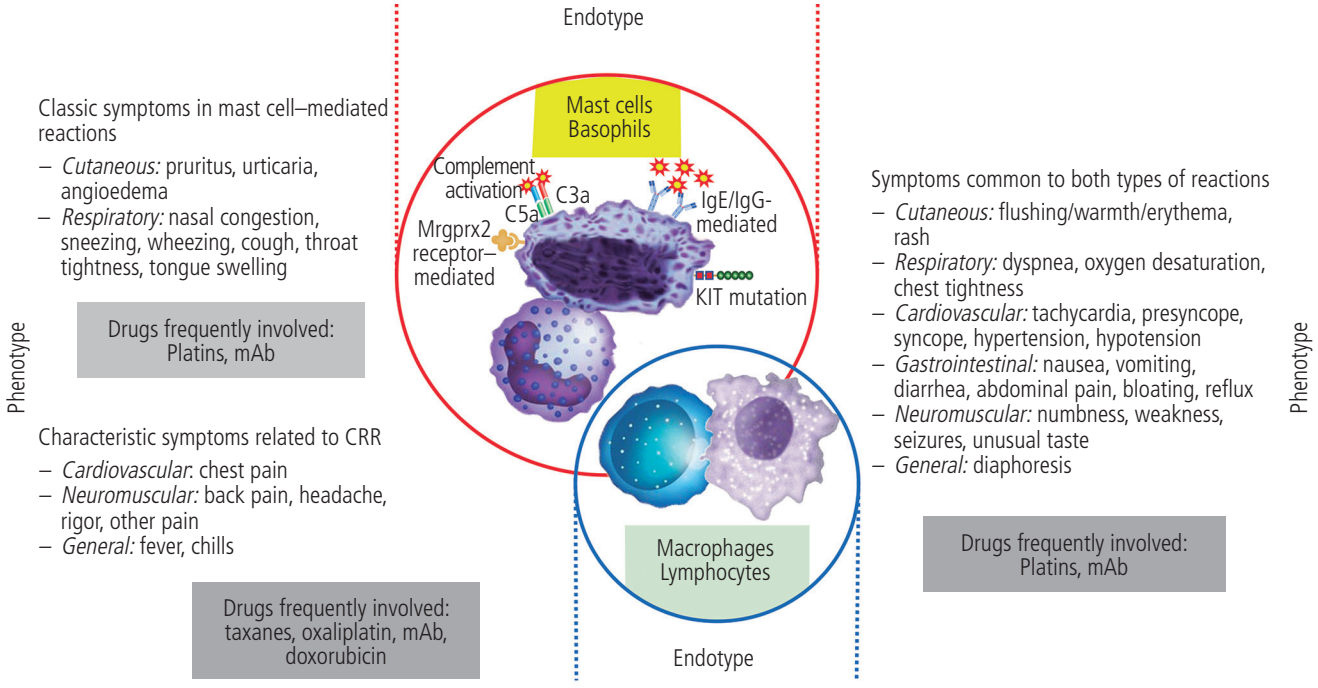

Figure 1. Phenotypes and endotypes of reactions to chemotherapeutic drugs and monoclonal antibodies. CRR indicates cytokine release reaction; mAb, monoclonal antibodies. Phenotype 2 includes symptoms of mast cell activation and symptoms that are common to other phenotypes. The CRR phenotype comprises characteristic symptoms of CRR and common symptoms. The mixed phenotype is a mixture of the above, and in the indeterminate phenotype there are only common symptoms.

necrosis factor alpha (TNF-α), interleukin (IL) 1β, and IL-6 can originate from multiple cellular sources, including T cells, monocytes, and macrophages [8,15] (Figure 1).

NIDHRs have been less studied and, phenotypically, range from nonsevere maculopapular exanthema (MPE) to severe reactions (eg, Stevens-Johnson syndrome [SJS] and 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 T-cell activation, as described with agents such as temozolomide, rituximab, infliximab, and taxanes [16-18]. Recently, the "converter phenotype" was described in patients treated with taxanes who presented NIDHRs and in subsequent exposures developed IDHRs, generally type 1 reactions [19].

Table 1. Brown Classification of Hypersensitivity Reactions

Grade	Severity	Description
1	Mild (skin and subcutaneous tissues only)[a]	Generalized erythema, urticaria, periorbital edema, or angioedema.
2	Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain.
3	Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or SpO_2 ≤92% at any stage, hypotension (SBP < 90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence.

Adapted from Brown SGA [20].
Abbreviations: SBP, systolic blood pressure; SpO_2, oxygen saturation.
[a]Mild reactions can be further subclassified into those with and without angioedema.

2.2. Classification of Severity

Of the various proposals for organizing severity of DHRs, that of Brown [20] (Table 1) is the most straightforward because it is quick and easy to apply. Recently, Madrigal-Burgaleta et al [21] published a new, more extensive and detailed classification, known as the "Ramon y Cajal University Hospital (RCUH) classification for DHR" (Table 2). While both are useful, RCUH includes a broader spectrum of symptoms related to various DHR phenotypes, and severity is classified according to the time of onset of the reaction.

Box 1. Practical Recommendations

- DHRs are classified as immediate or nonimmediate depending on 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 DHRs, with emphasis on desensitization.
- Classification of severity is important when stratifying risk, approaching the allergology work-up, and guiding therapeutic management.

3. Antineoplastic agents

3.1. Chemotherapeutic Agents

Any antineoplastic agent can potentially induce DHRs. The agents most frequently involved are presented below:

3.1.1. Platinum salts

DHRs to platinum compounds are most often IgE-mediated, although non–IgE-mediated or mixed reactions have also been reported [22,23]. 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

Table 2. Ramon y Cajal University Hospital Classification for Drug Hypersensitivity Reactions

Mild reaction	Moderate reaction	Severe reaction	Anaphylactic shock
Erythema Pruritus Local urticaria/angioedema Fever/chills (<38ºC) Mild back pain	– Slow onset (>15 min): Generalized urticaria/angioedema Coryzal symptoms Irritative cough Dyspnea (SpO_2 >92%) Throat tightness Nausea Abdominal pain Severe back pain Fever (>38ºC)	– Rapid onset (<15 min) General urticaria/ angioedema Coryzal symptoms Irritative cough – and/or manifestation of Throat tightness with dysphagia and/or dysphonia and/or stridor Wheezing Chest tightness Vomiting Diarrhea SpO_2 <92% Diaphoresis Dizziness Hypertension	– Immediate onset (or rapid progression) of any of the latter and manifestation of any of the following: Hypotension Cyanosis Sense of impending doom Faintness Loss of sphincters control Cardiovascular and/or respiratory arrest

Adapted from Brown [20].

those with at least 15 cycles experience a reaction [25,26]. Similarly, the incidence of oxaliplatin reactions ranges from 7.1% in the first 6 cycles to 20.6% when patients receive more than 6 cycles, with most reacting during the seventh to ninth infusion [27]. However, patients who develop cytokine release reactions with oxaliplatin usually react during the first exposures [13]. Similar findings have been reported for 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, with MPE being the most frequent [31]. Cases of antibody-mediated thrombocytopenia, delayed urticarial vasculitis [28,32], and pulmonary fibrosis have also been reported [33].

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

Table 3. Characteristics of Hypersensitivity Reactions to Cancer Chemotherapy (Other Than Taxanes and Platinum Compounds)

Drug	Mechanism	Type	Indications	DHR	References
Chemotherapeutic drugs					
Cyclophosphamide	Nitrogen mustard alkylator	Alkylating agent	HL, leukemia, ovarian and breast cancer	Rare IDHR: IgE-mediated (apparently to the active metabolite) Rare NIDHR: MPE	[3,5,160,161]
Gemcitabine	Nucleoside metabolic inhibitor	Analog of deoxycytidine	Ovarian, breast, NSLC and pancreatic cancer	Rare IDHR: IgE-mediated NIDHR: MPE, TEN, SJS	[5,21,162-164]
Irinotecan	Topoisomerase inhibitor	Enzyme inhibitor	Colorectal cancer	Rare IDHR: IgE-mediated	[21,73,165]
Fluorouracil	Nucleoside metabolic inhibitor	Antimetabolite	Breast, colorectal, gastric and pancreatic cancer	Rare IDHR: IgE-mediated Rare NIDHR: MPE	[166]
Monoclonal antibodies					
Rituximab	CD20	Chimeric	NHL and CLL	IDHR: IgE-mediated and CRR. NIDHR: SSR, TEN, SJS	[14,50-54,167]
Cetuximab	EGFR	Chimeric	Head and neck cancer and colorectal cancer	IDHR: IgE-mediated and CRR	[55,56,168,169]
Trastuzumab	HER 2	Humanized	Breast cancer, gastric and gastroesophageal cancer	IDHR: IgE-mediated and CRR	[170-173]
Pertuzumab	HER 2	Humanized	Breast cancer	IDHR: IgE-mediated	[174]
Bevacizumab	VEGF	Humanized	Colorectal cancer	IDHR: IgE-mediated and CRR	[175,176]
Brentuximab	CD30	Chimeric	SALCL, HL	IDHR: IgE-mediated and CRR	[18,94,177-179]
Nivolumab	PD-1	Human	Melanoma, NSLC, renal cancer, HL, neck and head cancer, HCC	IDHR: IgE-mediated NIDHR: MPE	[123,180,181]

Abbreviations: CLL, chronic lymphocytic leukemia; CRR, cytokine release reactions; DHR, drug hypersensitivity reaction; EGFR, epidermal growth factor receptor; mAb, monoclonal antibody; HCC, hepatocellular cancer; HER 2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; IDHR, immediate drug hypersensitivity reaction; MPE, maculopapular exanthema; NIDHR, nonimmediate hypersensitivity reactions; NHL, non-Hodgkin lymphoma; NSLC, non–small cell lung cancer; SALCL, systemic anaplastic large cell lymphoma; SJS, Stevens-Johnson syndrome; SSR, serum sickness-reactions; TEN, toxic epidermal necrolysis; VEGF, vascular endothelial growth factor.

3.1.2. Taxanes

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

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

3.1.3. 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 initial 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 chemotherapeutic drugs, such as cyclophosphamide, gemcitabine, irinotecan, and fluorouracil, are rarely involved in DHRs. We provide extended information about these in Table 3.

Table 4. Recommended Drug Concentration Used for Skin Testing With Cancer Chemotherapy

Drugs	Concentration, mg/mL SPT	IDT 1	IDT 2	IDT 3	References
Chemotherapeutic drugs					
Platins					
Cisplatin	1	0.1	1		[3,90]
Carboplatin	10	1	10		[3,90]
Oxaliplatin	5	0.5	5		[3,90]
Taxanes					
Paclitaxel	6	1			[70,142]
Docetaxel	10	1	10		[70,90]
Other chemotherapeutic agents					
Doxorubicin	NR	NR			[182]
Cyclophosphamide	10	1	10		[5,73]
Gemcitabine	38	3.8	38		[73]
Irinotecan	20	2	20		[73]
Fluorouracil	0.01	0.001	0.01		[166]
Monoclonal antibodies					
Rituximab	10	0.1	1		[14,52,183]
Cetuximab	5	0.5	5		[14,168]
Trastuzumab	21	2.1			[14,48,52]
Pertuzumab	1.6	0.16	0.016		[94]
Bevacizumab	25	2.5	25		[5]
Brentuximab	25	0.025	0.25	2.5	[94]
Nivolumab	1	0.1			[123]

Abbreviations: SPT, skin prick test; IDT, intradermal test; NR, not recommended.

3.2. Monoclonal Antibodies

The degree of humanization and other factors related to the monoclonal antibody or the disease treated may affect the immunogenicity of a biological drug [47]. Even fully human proteins can elicit an immune response, producing antidrug antibodies and DHRs [48]. Antidrug antibodies may not only shorten drug half-life, but also mediate mild to serious DHRs [47,48]. For this reason, DHRs are common with some biologics, for example, rituximab or trastuzumab [18,49].

Reactions to monoclonal antibodies are usually phenotype 1, and a change to the cytokine release reactions phenotype may occur during desensitization. Moreover, while it is not entirely clear why, standard premedication may block mast cell activation but not the symptoms induced by cytokines [14].

3.2.1. Rituximab

Rituximab is a chimeric murine/human IgG1 kappa monoclonal antibody targeting CD20. It is indicated for the treatment of patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia [50]. Rituximab is commonly associated with cytokine release reactions 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 have been reported [53,54].

3.2.2. Cetuximab

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

3.2.3. Other monoclonal antibodies

Given the increasingly widespread use of monoclonal antibodies in the treatment of neoplastic, autoimmune, and inflammatory diseases, many have been implicated in DHRs, and case reports are becoming more frequent (see Table 3 for additional information).

3.3. Protein Kinase Inhibitors

Protein kinase inhibitors are a new approach to cancer treatment with targeted therapy. The incidence of DHRs to these agents 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 nonimmediate urticaria [62-64], although some cases of SJS induced by regorafenib (vascular endothelial growth factor receptor inhibitor), ribociclib, and palbociclib (cyclin-dependent protein kinase inhibitors) have been described [65,66].

Cross-reactivity has been reported between dabrafenib and vemurafenib, as both target B-Raf inhibitors and have similar chemical structures [67].

4. Allergological Study

4.1. Skin Tests

Skin prick tests with chemotherapeutic drugs and monoclonal antibodies should be performed at full strength, followed, if negative, by an intradermal test using serial dilutions (Table 4). The results should be interpreted at 15-20 minutes, and after 24 and 72 hours if an NIDHR is suspected [68]. Although 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 skin testing can affect the results. Therefore, testing should be performed at least 4 to 6 weeks after and within 6 months of the reaction to avoid false-negative results [70,71]. Negative controls should be included, if possible when using dilutions of uncertain significance [72].

4.1.1. Platins

Skin testing with oxaliplatin has a high positive predictive value and low negative predictive value (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 routine skin testing to platins after the sixth cycle in patients receiving their first line of treatment or after the second cycle in patients receiving their second line of treatment, especially if there is a treatment-free period. In the case of a positive skin test result, the platin 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 skin test results [76].

4.1.2. Taxanes

The negative and positive predictive values are unknown. Positive results in skin testing with these drugs vary according to the geographical area studied, and it has been suggested that some patients may be sensitized to yew tree pollen, an environmental allergen. In addition, owing to cross-reactivity, IgE-mediated IDHR can be observed at first exposure [77,78].

4.1.3. Drugs not to be used in skin tests

Skin tests should not be performed with some antineoplastic agents, such as anthracyclines, vinblastine, vincristine, mitomycin C, and mechlorethamine, which are vesicants [72].

Table 4 shows the most widely used concentrations in skin tests with chemotherapeutic drugs and monoclonal antibodies, which have been shown to be nonirritant.

4.2. In Vitro Tests

4.2.1. Biomarkers

4.2.1.1. Tryptase

Tryptase levels increase from 15 minutes to 3 hours, with a peak about 120 minutes, after onset of the reaction [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 determination increases the sensitivity of tryptase as a biomarker [80], and applying the formula (baseline × 1.2)+2, especially if basal tryptase levels are low, makes it possible to identify patients with MC activation even if the limit of 11.4 ng/mL is not exceeded [81-83]. In patients with a baseline tryptase level >7.5 ng/mL, tryptase genotyping should be considered. An increased α-tryptase gene copy number was observed in a recently described syndrome called hereditary alpha tryptasemia, which has also been linked to a higher risk for hypersensitivity reactions [84-86].

4.2.1.2. Cytokines

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

4.2.1.3. Total IgE and specific IgE

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

Diagnosis of DHR to platinum compounds has been studied in large samples of patients, making it possible to establish the diagnostic yield of specific IgE (sIgE) to these agents. This approach has 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 1 patient [91].

4.2.2. Basophil activation test

Several studies have evaluated the value of the basophil activation test (BAT) in the diagnosis of DHRs to platins [23,71,92,93]. Giavina-Bianchi et al [23] recently estimated that BAT has a sensitivity of 73% and a specificity of 100% for DHRs to platins. The authors also observed higher CD63 expression in patients with severe breakthrough reactions during desensitization. The BAT could be used as a biomarker of risk before desensitization, although further studies are required to validate this technique.

In vitro diagnostic tests for DHRs to monoclonal antibodies are generally not standardized, although they have been performed in some case reports [94]. More studies with larger samples of patients are needed to establish the usefulness of BAT with monoclonal antibodies as a diagnostic tool.

4.3. Drug Provocation Test

DPT is the controlled administration of a drug and is considered the gold standard for confirming or ruling out a diagnosis of hypersensitivity [95-97]. DPT should only be performed under the most rigorous medical supervision and taking the same precautions and considering the same

contraindications established for other drugs in international guidelines [95-98].

DPT prior to desensitization has rarely been used as a diagnostic tool in DHRs to chemotherapeutic drugs and monoclonal antibodies [21,70,73,78,90]. In the largest reported series, 341 DPTs were performed in patients with mild or moderate DHRs and a negative skin test result [21]. The authors reported negative DPT results in 67% of tests, corresponding to 44% of all patients; 69% were with taxanes, 46% with platins, and 78% with biological agents. Indeed, only 15% of the positive DPTs involved a severe reaction. These results suggest that performing DPT before desensitization may exclude hypersensitivity in some cases and avoid unnecessary desensitization.

The methodology for DPT with chemotherapeutic drugs and monoclonal antibodies reported by Madrigal-Burgaleta et al [21,73,90] involves the administration of the culprit drug according to manufacturer's instructions and institutional protocols [95-97], including standard premedication and additional necessary medications (eg, other antineoplastic drugs, leucovorin). Indeed, ß-adrenergic blocking medications must be withheld for 24 hours before the DPT. The patient's scheduled treatment is used to perform the DPT to avoid delays or overdose. In the case of a positive DPT, the infusion should be withheld and the DHR treated according to severity [20,21]. Once the symptoms have resolved, usually within 30 minutes, the infusion can be restarted at one quarter of the final infusion rate for 15 minutes, and then increased to half until all the medication is administered ("restart protocol"). All patients with a negative DPT result must be closely supervised during subsequent standard drug administrations.

DPTs with other drugs, such as premedication, concomitant drugs, additional chemotherapeutic drugs, and monoclonal antibodies possibly involved in the initial reactions should be performed before DPT with the culprit drug [21,73,90,99].

Castells et al [70] also reported a progressive approach to reintroduction of taxanes in 49 patients with negative skin test results and grade 1-2 IDHRs and mild NIDHRs. The protocol included premedication with montelukast, aspirin, and/or zileuton. The infusion started at 10 mL/h and increased progressively to 160 mL/h in 10-fold increments between steps, with a final infusion rate equivalent to a regular infusion [70]. All procedures were performed in the desensitization unit with 1 nurse per patient. Only 3 patients had a reaction: 2 (4%) experienced a grade 1 reaction, and 1 (2%) a mild delayed reaction.

Recently, Martí-Garrido et al [100] published tolerance to chemotherapeutic drugs and monoclonal antibodies during DPT in 22/23 patients with mild reactions and negative skin test results, disregarding the need for desensitization in 24% of their patients.

Finally, in a recent multicenter study by the European Network of Drug Allergy [78], 16 patients with grade 1 reaction to paclitaxel or docetaxel and negative skin test results underwent a DPT. The culprit drug was administered at 10 mL/h for the first hour and the remainder according to the manufacturer's instructions. DPT was well tolerated by all patients.

Box 2. Practical recommendations

- Skin tests are useful for identifying immediate, probably IgE-mediated reactions and also for NIDHRs when the reading is delayed. 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 cytokine release reactions.
- DPT is the gold standard for confirming or ruling out DHRs to chemotherapeutic drugs and monoclonal antibodies. Performing DPT before desensitization optimizes patient management, since it may avoid unnecessary desensitization.
- DPT is a high-risk procedure that requires proper patient selection, an experienced allergist, and a suitable setting prepared for possible reactions during the procedure.

5. Drug Desensitization

5.1. Biological Principles of Desensitization

In vitro models of rapid IgE desensitization show that sensitized mast cells become unresponsive to the allergen under the following conditions: (*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- to 2.5-fold at each step [4,101,102]. Desensitized mast cells demonstrated almost complete inhibition of immediate release of β-hexosaminidase, early and late release of TNF-α, production of IL-6, de novo synthesis of lipid mediators, calcium influx, and activation of arachidonic acid metabolism [102-104], thus leading to the inhibition of both the early and late mast cell responses. Additionally, desensitization impairs internalization of the antigen/IgE/FcεRI complexes [103,105] and induces a decrease in 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, thus potentially upsetting the balance between the 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. This process is reversible over 2-3 days, depending on pharmacokinetic parameters [106]. Successful desensitization has been related to the increase in IL-10 [109]. The mechanism of rapid desensitization to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is thought to differ from that of chemotherapeutic drugs and monoclonal antibodies and is based on decreased production of leukotrienes and tryptase [110].

5.2. Patient Selection

Rapid drug desensitization (RDD) can be performed in patients of any age. It can also be performed 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 used successfully in patients with different phenotypes of IDHRs, and in NIDHRs it is restricted to MPE or fixed drug eruption (FDE) [11,98].

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

5.3. Risk Stratification

Mild symptoms and negative skin test results are associated with a lower risk of reaction, while moderate-to-severe symptoms and/or positive skin or serological test results indicate higher risk [3,4,23,70]. Other factors such as comorbidities (eg, heart disease or severe respiratory failure), use of concomitant medications that may interfere with the treatment of a possible reaction, such as ß-blockers, must be assessed when stratifying risk [2].

Based on the RCUH classification for DHRs to chemotherapeutic drugs and monoclonal antibodies [21] (Table 2) and the presence of patients and/or hospital-related factors (Table 5), we propose a risk stratification algorithm for RDD (Table 6) and its management (Table 7).

5.4. Rapid Drug Desensitization Protocols: Efficacy and Safety

5.4.1. Immediate Reactions

Several intravenous and subcutaneous desensitization protocols for IDHR to chemotherapeutic drugs and monoclonal antibodies have been reported [5,14,52,70,90,114-119]. The Brigham and Women's Hospital group (BWH) reported the largest worldwide series of 2177 RDDs with chemotherapeutic drugs and monoclonal antibodies using rapid multisolution and multistep protocols administered over 5.7 hours [3,5,117,120]. A 3-bag/12-step protocol based on an in vitro mouse bone marrow–derived mast cell model has also been reported [102,103]. The protocol starts at a concentration of 1/100, with a fold increase of 2 to 2.5 in each step and an interval of 15 minutes between them. This is a flexible protocol that must be individualized according to risk and can be lengthened (4-bags/16-steps) in high-risk patients

Table 5. Concomitant Conditions to Consider in Risk Stratification for Desensitization

Patient's condition	Institutional conditions
Uncontrolled asthma or lung disease	*Nurses*
Acute heart disease	More than 2 patients per nurse
Mastocytosis	No specially trained staff
Unavoidable use of ß-blockers	*Allergist*
Pregnancy	No access to expert allergists in <2 min
Acute infections	*Institutional factors*
Critically ill patient	There are no specific areas to perform this technique
	Difficulties managing breakthrough reactions

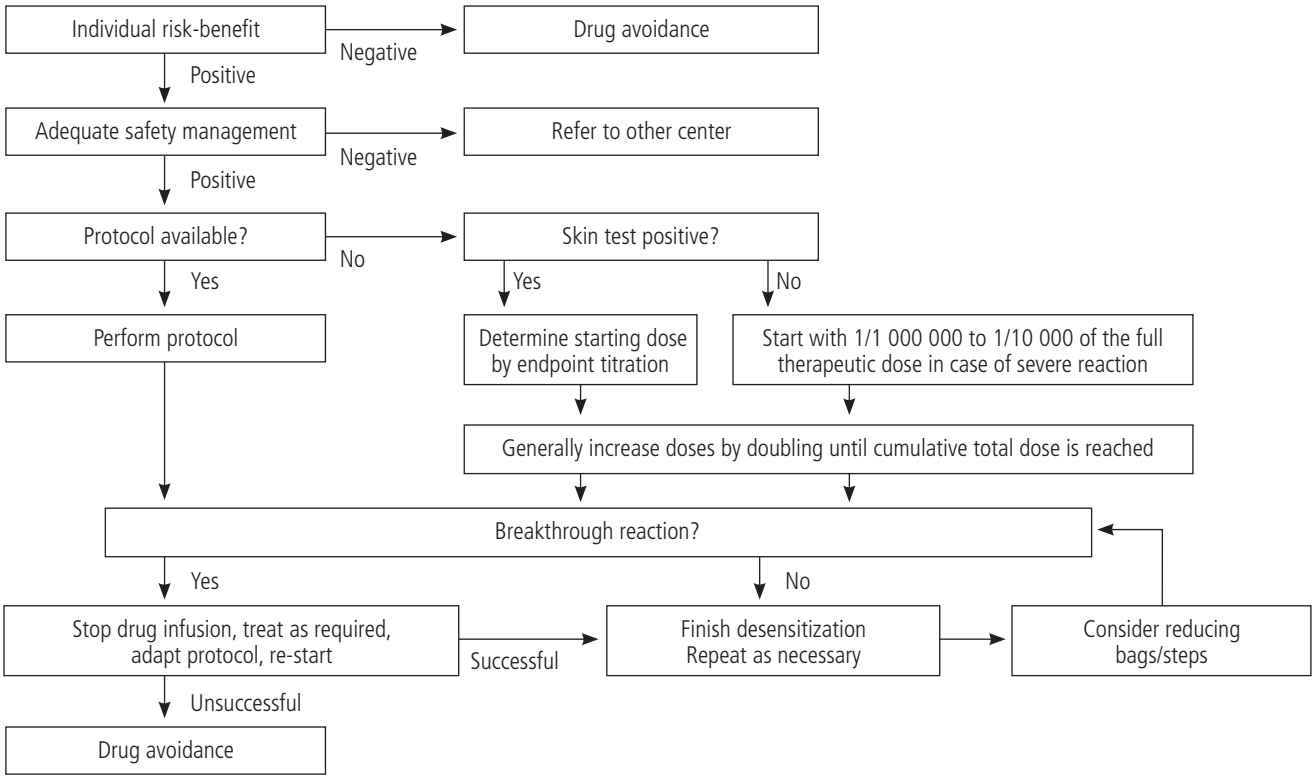

Figure 2. Algorithm for conducting drug desensitization. Adapted from Cernadas et al [2].

Table 6. Risk Stratification Proposal[a]

Low risk	Medium risk	High risk
Grade I	Grade II	Grade III / IV
No patient or institutional conditions	Grade I and – 1 patient condition or – 1 institutional condition	Grade II and – 1 patient condition or – 1 institutional condition or – Positive results in the allergological study
	Grade I and - Positive results in the allergological study	Grade I and – 1 patient condition and – 1 hospital condition and/or – Positive results in the allergological study
		Grade I and – 2 patient condition or – 2 institutional condition

[a]Considering the severity of the initial drug hypersensitivity reaction, results of the allergological study, and the presence of concomitant conditions. The reaction grade is based on the Ramón y Cajal University Hospital classification for drug hypersensitivity reactions [21].

Table 7. Management Proposal Based on Risk Stratification

Low risk	Medium risk[b]	High risk
DPT or supervised regular administration[a]	Drug desensitization Recommended setting: ADCU Starting dose: 1/100 No. of steps: 8-12	Drug desensitization Recommended setting: ICU and/or ADCU[c] Starting dose: 1/10 000-1000 No. of steps: 12-16

Abbreviations: ADCU, allergy day care unit; DPT, drug provocation test; ICU, intensive care unit.
[a]In the DPT, increasing doses of the medication are given until a cumulative dose equal to the usual one is reached, while supervised regular administration is to repeat the administration of the drug, as normal, under medical supervision.
[b]Some medium-risk patients with negative results in the allergological study can be treated as low-risk, after a personalized evaluation.
[c]The choice of the desensitization site will depend on the number of patients and the institutional conditions in each case.

or shortened (2-bags/8-steps, 1-bag/4-steps) depending on tolerance and the initially estimated risk [14,70]. Indeed, this protocol enables the final rate to be reached in cases where there are no breakthrough reactions [4,5].

Based on the BWH protocol, several others have been published using different dilutions, fold increments, and premedication. All of them share a high degree of success and a low rate of breakthrough reactions (Table 8).

Madrigal-Burgaleta et al [90] published a 3-bag/10-step protocol for the first time in 2013 and a large series of 1050 desensitizations in 2019 [21]. The 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 the stability of the dilution. Perez-Rodriguez et al [121] demonstrated the safety of this approach in 490 desensitizations with different chemotherapeutic drugs and monoclonal antibodies. In this protocol, the infusion rate began at 5 mL/h with increases every 15 minutes up to 125-250 mL/h, which was the maximum infusion rate recommended by the manufacturer/oncologist.

Multiple protocols have been reported as single cases with few desensitizations for various chemotherapeutic drugs and monoclonal antibodies such as brentuximab vedotin [121,122], nivolumab [123], alemtuzumab [124,125], atezolizumab [126], bevacizumab [126,127], denosumab [128], daratumumab [129], and canakinumab [130]. The potential utility for the reader and the off-label use of some monoclonal antibodies was addressed in a recent review of desensitization procedures performed with monoclonal antibodies used in rheumatology [131]. However, this aspect was beyond the scope of the present article.

5.4.2. Nonimmediate reactions

The EAACI position paper criteria for desensitization in NIDHRs for any drug [132] included the following: (*1*) drug therapy is essential/irreplaceable and more effective than alternatives; (*2*) no alternatives are available; (*3*) the 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 on short series owing to the lack of controlled studies/consensus on protocols. This limitation is even more evident for chemotherapeutic drugs and monoclonal antibodies.

Sloane et al [5] published the largest series of RDD in 112 patients with mild NIDHRs. Testing was performed very

Table 8. Desensitization Protocols

Bags	Steps	Duration, h	RDDs reported	Increment dose, fold	Dose interval, min	BTR% (severe%)[a]	Additional premedication	Drugs	Ref
3	12	5.7	2177	2-2.5	15	26 (15)	H1b, H2b, ASA, Mtk	Taxanes, platinum, mAb	[5]
3	12	5.7	1471	2-2.5	15	9.6 (5.7)	H1b, H2b	Taxanes, platinum, mAb	[88]
3	10	4.25	1050	2-2.5	15	12 (10)	ASA, Mtk	Taxanes, platinum, mAb	[21]
1	6-9	3.5	490	1.5-2	15	5.3 (12)	H1b, H2b, ASA, Mtk	Taxanes, platinum, mAb	[138]
1	13	3.4	211	2	15	16.1 (2.6)	H1b, H2b, Mtk	Paclitaxel	[184]
1	5	6.3	77	2	30	33 (0)	ASA, Mtk	Cetuximab	[21]
1	16	4.5	58	4.5	15 (30 min step 15 and 16)	1.7 (0)	H1b, H2b, ASA, Mtk, C	Carboplatin, taxanes	[116]
5	5	2-5	39	10	15	5 (100)	H1b, C	Taxanes, platinum	[118]
4	11	6.3	32	2-2.5	15 (16.25 min step 3 and 13.75 min step 6 and 9)	56 (12.5)	H1b, C	Oxaliplatin	[114]

Abbreviations: ASA, acetylsalicylic acid; BTR, breakthrough reactions; C, corticosteroids; H1b, H1 blockers; H2b, H2 blockers; mAb, monoclonal antibody; Mtk, montelukast; RDD, rapid drug desensitization.
[a]The information in brackets expresses the percentage of severe reactions out of total reactions.

successful following the same 3-bag/12-step protocol used in IDHRs. These protocols have also been used successfully in a patient with MPE by bendamustine, who had positive skin test results in the delayed reading [133].

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 [28,70,134]. Picard et al [70] observed that 20% of patients with NIDHRs with taxanes had an IDHR after a new exposure; onset of flushing ≤48 hours after infusion increased the risk of breakthrough reaction (both immediate or delayed) upon a new exposure. These same authors found that patients with mild NIDHRs were more likely to resume regular infusions, particularly those with negative skin test results. However, some of them experienced an IDHRs after tolerating 3 regular infusions, and, on re-evaluation, had positive skin test results.

Other desensitization protocols using different administration routes have been published. Oral desensitization with temozolomide and capecitabine was successful in a limited series of procedures with delayed MPE [16,135], using either a 1-day/3-concentration/13-step protocol, doubling doses every 30 minutes, or a 3-concentration/14-step protocol for temozolomide. In the case of capecitabine, the dose was increased gradually over 16 days.

Desensitization appears to be a safe and effective option for treatment of DHRs to some tyrosine kinase inhibitors (imatinib, crizotinib, sunitinib, sorafenib, alectinib, regorafenib, and dabrafenib) [58,61-64,67,136].

6. Optimizing drug desensitization

6.1. Identifying risk factors for breakthrough reactions

A common finding in series on RDD to chemotherapeutic drugs and monoclonal antibodies is the high success rate and both the low number and severity of breakthrough reactions [5,14,21,70,88,137,138]. However, despite being generally mild, reactions occur in up to 25% of cases [5,14,21,70,88,137,138]. The various risk factors differ partially from one series to another (see below).

Sloane et al [5] used a 3-bag/12-step protocol and observed breakthrough reactions in only 26% of 2177 RDD. These were mostly mild, immediate, and generally between steps 7 and 12. Most patients (60%) had no reactions during the first RDD, regardless of the initial severity of the DHR. In fact, 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] used a 3-bag/10-step protocol and observed breakthrough reactions in 12% of 1027 RDDs. These were mostly grade 1 with skin symptoms as the main manifestation. The associated risk factors were positive skin test results and atopy (RRR 4.01 [1.8-10.3] and 2.16 [1.6-14.1], respectively). Based on the breakthrough reactions observed during RDD, the authors suggested classifying patients into 3 groups: (*1*) first RDD reactors, usually with moderate to severe breakthrough reactions; (*2*) reactors after several uneventful RDDs, associated with no premedication, sensitization to

new drugs, or transition to shorter RDD protocols; and (*3*) breakthrough reactions manifesting as fever/chills, which may precede anaphylaxis.

In a series of 104 RDDs to monoclonal antibodies using a 3-bag/12-step protocol, Isabwe et al [14] recorded breakthrough reactions in 23% of cases; these were mainly grade 1 and mostly during the final step. They also observed that a positive skin test result was associated with type I reactions during RDD. Indeed, subsequent procedures decreased the risk of breakthrough reactions, reaching a plateau after 20 RDDs. In fact, the frequency of grade 2 reactions decreased from 25% to 3% when the first 5 were compared with more than 10 RDDs.

In a series of 138 RDDs using a 3-bag/12-step protocol with taxanes, Picard et al [70] observed breakthrough reactions in 21%. Several factors were evaluated, such as age, cancer type, severity of the initial reaction, and skin testing; however, only atopy was significantly associated (OR, 4.9 [2-22.8]).

Kang et al [137] performed 234 RDDs with several chemotherapeutic drugs and monoclonal antibodies using the 3-bag/12-step protocol and found, in contrast with other series, that breakthrough reactions were associated with the severity of the initial reaction and the administration of previous cycles of the same drug. Indeed, the severity of these breakthrough reactions was associated with both factors and 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 breakthrough reactions, particularly with platinum compounds. However, atopy, skin test results, and severity of the initial DHR were not included in the multivariate analysis.

6.2. 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 report routine 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 the patient experienced during the initial reaction [140], such as benzodiazepines for anxiety [21,88], as well as paracetamol, opioids, and other NSAIDs for fever, pain, rigor, and chills. Indeed, aspirin and montelukast 10 mg 2 days prior to desensitization are added, respectively, in patients who experience flushing and respiratory symptoms [5,21,88,140]. Breslow et al [141] demonstrated that adding drugs to H1b/H2b, successfully reduced the severity of reactions occurring during desensitization more effectively than methylprednisolone (0.5 vs 1.75).

Fluids and normal saline have also been used as additional premedication, mostly in cytokine release reactions. In 81 RDDs, Isabwe et al [14] showed that using normal saline in the routine schedule reduced the severity of the breakthrough reaction. Similarly, using fluids after breakthrough reactions during desensitization reduced the severity of new DHRs in subsequent RDD (from 1.3 to 0.35). The authors recommended, for cytokine release reactions, using 100 mL/h of normal saline between steps 1 and 11 and increasing to 250 mL/h during step 12.

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 or severity of breakthrough reactions when comparing RDD to

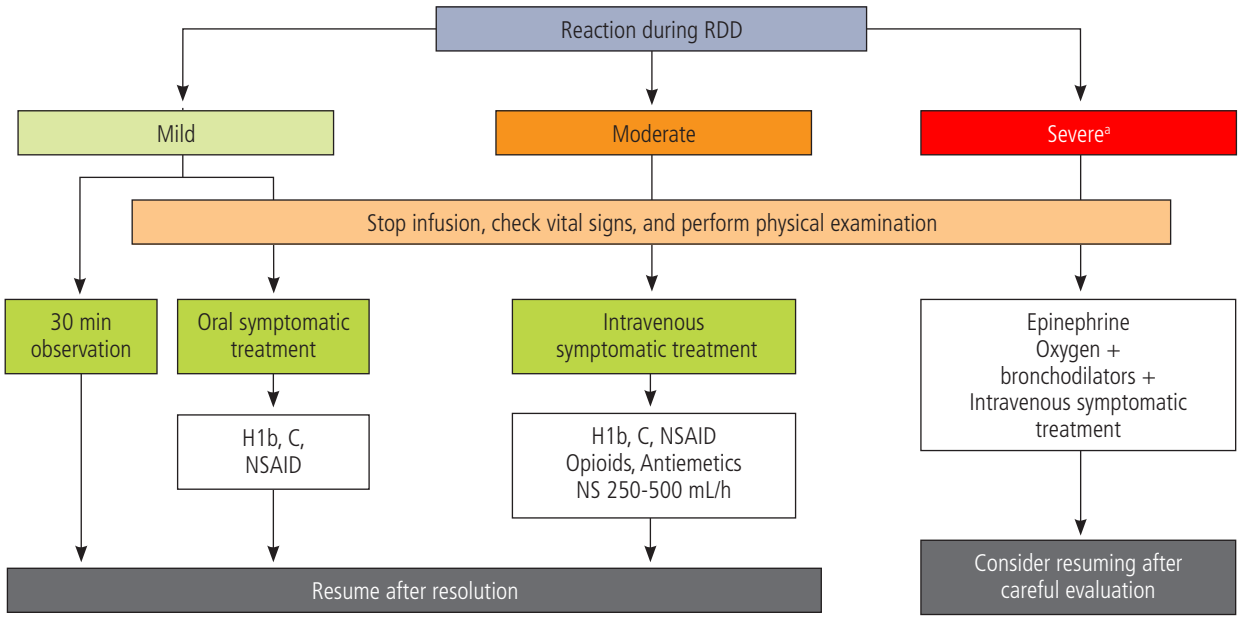

Figure 3. Management of reactions occurring during desensitization (breakthrough reactions). C indicates corticosteroids; H1b, h1 blockers; NS, normal saline; NSAID, nonsteroidal anti-inflammatory drug; RDD, rapid drug desensitization.
[a]Includes anaphylaxis and anaphylactic shock.

paclitaxel using corticosteroids combined with antihistamines as premedication in RDD without this premedication.

Avoidance of corticosteroids, unless they are required as an antiemetic or as part of an oncology protocol, is a common recommendation in most publications. As Breslow et al [141] showed, corticosteroids are less effective than aspirin or montelukast for preventing symptoms during RDD.

6.3. Handling Breakthrough Reactions

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

6.3.1. Immediate breakthrough reactions

Immediate breakthrough reactions are the most commonly reported in the literature because they are the most frequent (95%) [5,14]. Reactions usually appear in the final steps: steps 7-12 in the case of chemotherapeutic drugs and 12 for monoclonal antibodies [5]. A reaction occurring during the initial steps, that is, at a low dose, points to a patient with high reactivity.

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

Once symptoms have resolved, drug infusion can be resumed at the same step and infusion rate as when the reaction appeared [1,3,5,14,28,52,141,143]. Desensitization must be stopped only in the case of severe reactions—in agreement with the onco-hematology team—and postponed until further tailored changes in pretreatment and/or the protocol have been made.

After a breakthrough reaction during RDD, the premedication and protocol should be re-evaluated and customized based on the severity of the reaction, the step where it occurred, acute phase biomarker values (eg, tryptase, IL-6) if available, and the result of a new allergological evaluation. Recommendations for customizing subsequent RDD are summarized in Table 9.

Pretreatment with omalizumab may be considered when the abovementioned measures fail, although the quality of the evidence is low and many issues concerning optimal dose and pretreatment duration remain unanswered [144]. Case reports have been published with carboplatin (3 patients) [145,146] and oxaliplatin (5 patients) [21,147-149], and, while the authors used different approaches, outcomes were generally successful. In most, 300 mg omalizumab was used, and at least 1 dose was administered before desensitization was attempted.

6.3.2. Nonimmediate breakthrough reactions

The EAACI position paper on desensitization in NIDHR [132] states that there are insufficient data for recommendations on preventing delayed breakthrough reactions, although antihistamines, corticosteroids, and some immunosuppressants have been tested with different degrees of success. Published series of RDD to chemotherapeutic drugs and monoclonal antibodies provide almost no information regarding this issue, although a vague and empirical recommendation of using corticosteroids 2 to 7 days after RDD was made by Sloane et al [5].

Box 3. Practical Recommendations

- RDD is an allergen-specific procedure, ie, the molecular mechanisms of mast cell activation are rendered inactive only to the allergen used for desensitization.
- Risk of new severe reactions must be stratified based on the characteristics of the initial reaction and the result of the allergological study.
- IDHRs benefit greatly from RDD; multiple protocols (intravenous, subcutaneous, and 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 the case of breakthrough reactions.

Table 9. Potential Modification of Desensitization Protocols After Breakthrough Reactions

Possible modifications	References
New premedication based on BTR symptoms before the infusion or before the step where the reaction occurred	[1,3,14,88,140,141]
Change from 3-bag/12-step to 4-bag/16-step protocol in case of grade 3 reaction	[13,14]
NS as premedication, particularly in CRR	[13,14]
Temporary dose reduction	[13,14]
Adding intermediate steps	[1,3,88]
Lengthening final step	[13,14,88]
Premedication with omalizumab	[144,146,185]

Abbreviations: BTR, breakthrough reactions; CRR, cytokine release reaction; NS, normal saline.

7. Diagnosis and Rapid Drug Desensitizations in Clinical Practice

The goal of RDD is to achieve tolerance with the fewest possible adverse effects. The process of desensitization must be comprehensive and include the following [2,150,151]:

- Assessment of risks and benefits for the patient (risk stratification).
- Development of a protocol for the targeted drug and its implementation in appropriate facilities by trained personnel.
- Patient information and written consent.
- The evaluation of the potential breakthrough reaction (immediate or delayed) and subsequent planning of new tailored RDD when needed.

7.1. Work Circuit With a Multidisciplinary Team

It is essential to design a protocol to ensure the coordination of a multidisciplinary team including the medical services referring patients (eg, oncology, hematology, internal medicine), pharmacy, allergy, and nursing, as well as quality indicators to assess the functioning of the protocol. Allergists are responsible for assessing the patient with DHR and stratifying risk, deciding on the location of RDD, establishing the protocol and number of steps, and overseeing the process from the beginning. The allergist is ultimately responsible during drug administration. Nurses trained in allergy are responsible for conducting the skin tests and DPT, administering treatment, and implementing and supervising the RDD protocol (Figure 4). The patient must be fully informed about the DHR experienced, the allergological study, options for therapy, and the RDD process. The patient must give written informed consent for the procedures after all doubts have been resolved. The RDD work circuit and protocol should have received the approval of the institutional ethics committee.

7.2. Safety Recommendations for the Diagnosis and Desensitization of Cancer Chemotherapy

7.2.1. 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 breakthrough reactions, including anaphylaxis, the treatment of DHRs including cardiopulmonary resuscitation training, and the regulations on handling cytostatic drugs [2,152,153]. There should be 1 nurse per patient, especially for those who have had severe reactions [46].

Chemotherapeutic drugs and monoclonal antibodies 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. Therefore, 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].

It is also important to know whether the individual infusion line (usually 22 mL) has been primed with the chemotherapeutic drug or with the diluent so that intermediate steps can be scheduled if necessary [90].

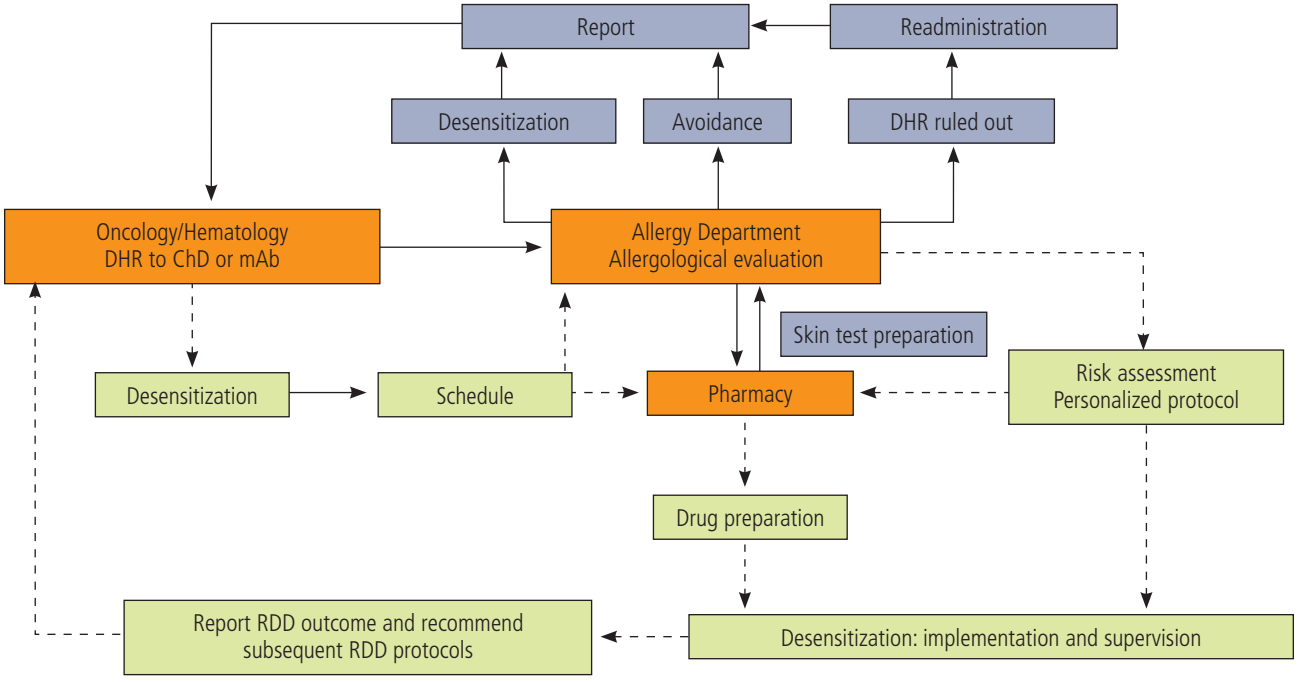

Figure 4. Evaluation of a drug hypersensitivity and desensitization circuit. DHR indicates drug hypersensitivity reactions; RDD, rapid drug desensitization; ChD, chemotherapeutic drug; mAb, monoclonal antibody.

7.2.2. Specific resources and adequate surveillance setting

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

In high-risk patients, RDD may be performed in an ICU to minimize risks. Once a successful procedure has been completed, the 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].

7.2.3. Safe handling of antineoplastic and biological agents in allergy units

The antineoplastic and biological agents involved in DHRs are considered hazardous drugs [156]. Allergy units must have specific written protocols that include a list of hazardous drugs used and appropriate personal protective equipment according to the diagnostic and therapeutic procedure [90,157]. All staff handing hazardous drugs must demonstrate proficiency before handling them and at least every 12 months thereafter [158]. The recommendations below are based on various guidelines [156,157,159].

7.2.4. Personal protective equipment

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

7.2.5. Guaranteed safe work practices and accidental hazardous drug exposure action plan

Chemotherapeutic drugs and monoclonal antibodies require special handling owing to the risk of breathing aerosol, splashing drops, and skin contact during diagnostic and therapeutic procedures. The proper and safe use of each element of personal protective equipment depends on the procedure performed and is detailed in Table 10. Chemotherapeutic drugs must be handled in a dedicated workplace, with a spill kit and hazardous drug waste container readily available. Syringe preparations for skin tests must have Luer-Lock connections to prevent spills. During DPT and desensitization, closed transfer system devices and preparations with valve systems with the connector incorporated should be used. Hazardous waste (lancets for skin tests, syringes, drug bags, tubing, protective equipment) must be placed in a container clearly identified with the cytotoxic hazard symbol. A spill kit and written recommended steps for the spill clean-up procedure should be readily available within the work areas where skin tests, DPT, and desensitization are performed.

Box 4. Practical Recommendations

- Successful RDD requires a multidisciplinary team including physicians, pharmacists, and 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, preparation of RDD protocols, supervision of the procedures, and modification of the protocols in the case of a breakthrough reaction.
- 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 drugs involved in DHRs are considered hazardous. All the staff involved in desensitization must be trained in the use of personal protective equipment to handle these drugs and work in safe areas that have action plans for accidental exposure.

Key messages

- DHRs must be assessed by trained allergists who should personalize diagnostic and therapeutic options in patients with cancer.

Table 10. Personal Protective Equipment According to the Procedure[a]

	PPE			
Procedure	Gloves	Gowns	Mask	Goggles
Skin test	Yes (double)	Yes	Yes	Yes
Intravenous administration with CTS	Yes	No	No	No
Intravenous administration without CTS	Yes	Yes	Yes	Yes
Intramuscular administration	Yes	Yes	Yes	Yes
Subcutaneous administration	Yes	Yes	Yes	Yes
Oral administration (tablets)	Yes	No	No	No
Oral administration (suspension)	Yes	Yes	Yes	Yes

Abbreviations: CTS, closed transfer system device; PPE, personal protective equipment. [a]Adapted from Power et al [157].

– RDD is an effective and safe option that enables patients with DHR to continue first-line treatment.
– A multidisciplinary team and appropriate facilities and clinical resources should be available prior to performing RDD.

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Conflicts of Interest

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