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REVIEW ARTICLE

Drug Desensitization in the Management of Hypersensitivity Reactions to Monoclonal Antibodies and Chemotherapy

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Abstract Hypersensitivity reactions to monoclonal antibodies and chemotherapy, which may vary in severity from mild to life-threatening, can lead to their discontinuation and replacement by alternative agents that are often less effective, more toxic, and/or more expensive. Drug desensitization has emerged as the best treatment modality capable of allowing re-introduction of the hypersensitivity reaction-inducing medication in highly sensitized patients in need of first line therapies. In recent years, the availability of new anti-neoplastic drugs and therapeutic monoclonal antibodies has increased, as has the potential for hypersensitivity reactions. Development of desensitization protocols for these new medications requires a careful assessment of the potential risks and benefits. The purposes of this review are to provide an overview of the presentation of hypersensitivity reactions amenable to desensitization and to increase awareness of the indications for and outcomes of desensitization protocols. Rapid drug desensitization has proven to be a safe and effective way of administering first line therapy to patients with hypersensitivity reactions, providing an extremely powerful treatment modality for patients for whom alternative drugs are deemed unacceptable. Rapid drug desensitization protocols should be administered only by highly trained allergists and nurses who have experience in determining which reactions are amenable to desensitization, and can identify high risk patients and provide them with appropriate care. Efforts should be made to increase awareness of the remarkable safety and efficacy of rapid drug desensitization among non-allergists, especially in the fields of oncology and rheumatology, so as to favor its universal application. Development of desensitization units to provide state-of-the-art care is possible only through coordinated teamwork.

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1 Introduction

Over the last 20 years, major advances have been made in the treatment of cancer, as well as autoimmune and chronic inflammatory diseases, through the development of targeted therapies, such as monoclonal antibodies, and routine use of multiple-drug combination regimens. This therapeutic approach has improved disease outcomes, quality of life, and survival rates [1]. However, hypersensitivity reactions (HSRs) to these molecules, which may vary in their severity from mild to life-threatening, can lead to their discontinuation and replacement by alternative agents that are often less effective, more toxic, and/or more expensive. HSRs are increasing in frequency in patients exposed repeatedly to monoclonal antibodies or multiple courses of chemotherapy, presenting a challenge to both physicians and patients, since they occur unexpectedly and their symptoms may be atypical, leading to a delay in diagnosis. Drug desensitization has emerged as the best treatment modality capable of allowing re-introduction of the HSR-inducing medication in highly sensitized patients in need of first line therapies.

The purposes of this review are to provide an overview of the presentation of HSRs amenable to desensitization and to increase awareness of the indications for and outcomes of desensitization protocols for chemotherapy and monoclonal antibodies.

2 Overview of Hypersensitivity Reactions

According to the World Health Organization (WHO), adverse drug reactions (ADRs) are defined as undesirable and unintended reactions occurring due to the use of a particular drug for prophylactic, diagnostic, or therapeutic purposes [2]. Drug HSRs are a subgroup of ADRs that are unexpected and are characterized by objectively reproducible symptoms and/or signs initiated by exposure to a drug at a dose that is normally tolerated [3].

The current classification of HSRs includes immediate and non-immediate reactions, based on the symptoms and the time between the administration of the medication and their onset [4, 5]. Immediate HSRs occur while the medication is being administered (such as during the infusion of chemotherapy) or within the first hour after administration, and they are clinically characterized by flushing, urticaria, angioedema, laryngeal edema, gastrointestinal symptoms (nausea, vomiting, diarrhea), respiratory symptoms (rhinoconjunctivitis, bronchospasm), and anaphylaxis, with or without cardio-vascular collapse, which can lead to death. Non-immediate HSRs can occur from an hour to several days after administration, and they include clinical manifestations such as maculopapular rashes, fixed drug eruptions, vasculitis, erythema multiforme, Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DiHS)—also known as drug reaction with eosinophilia and systemic symptoms (DRESS)—and acute generalized exanthematous pustulosis (AGEP).

Severe immediate HSRs can present as anaphylaxis, which is defined as a serious, life-threatening, systemic hypersensitivity reaction, which is rapid in onset and can result from immunoglobulin-E (IgE) and non-IgE mechanisms [6]. Its diagnosis is based primarily on a detailed clinical history, and its severity is graded from I (mild reaction) to V (death) by the Systemic Reaction Grading System of the World Allergy Organization [7–9]. Although the diagnosis of anaphylaxis is based on clinical features, measurement of serum tryptase, a mast cell granule protease released at the time of cell activation and degranulation, helps to confirm it [10]. Anaphylaxis is potentially fatal and should be treated promptly with intramuscular epinephrine, as delays in treatment are associated with an increased mortality rate [6].

Immediate HSRs specific to monoclonal antibodies and chemotherapy, which result from mast cell and/or basophil activation, cause symptoms that range from flushing and urticaria to anaphylactic shock, and can be associated with an elevated serum tryptase [11–13]. Monoclonal antibodies can cause HSRs through cytokine release, presenting with fever, chills, respiratory symptoms (shortness of breath), and gastrointestinal symptoms (nausea, vomiting, diarrhea) [12].

3 Rapid Drug Desensitization Principles and Mechanisms

Rapid drug desensitization (RDD) is a procedure that allows safe re-administration of a drug to which a patient has become allergic, and it is performed when no alternative to that drug is deemed equally effective. In recent years, RDD has been performed routinely in a few specialized centers worldwide, where it is handled by experienced allergists and nurses, with remarkable safety and efficacy [11, 12, 14]. In those centers, RDD has become standard-of-care for those patients who have become allergic to the chemotherapeutic drug or monoclonal antibody that is considered first line treatment for their underlying disease.

RDD protocols provide incremental doses of medication until the target dose is reached, starting with a dose well below the threshold for mast cell activation and therefore protecting the patient against anaphylaxis. The initial dose is doubled at fixed time intervals (typically every 15 min), and the target dose is reached within a few hours (Tables 1, 2) [11, 12]. Importantly, RDD needs to be repeated at each infusion, as this desensitization is temporary. The cellular mechanisms of RDD are not completely understood, but in vitro models have provided the basis for RDD protocols [15].

Mast cells (MCs) and basophils are the key cells participating in immediate HSRs to drugs. Both tissue-resident mast cells and circulating basophils express on their surface the IgE high affinity receptor (FcεRI) to which drug-specific IgE is bound. MCs and basophil mediators, contained in their granules, are released following FcεRI dimerization, which happens upon the binding of the drug to its specific IgE [16, 17]. Mediators such as histamine, leukotrienes (LTs), prostaglandins (PGs), and cytokines (tumor necrosis factor [TNF]-α and interleukin [IL]-6) bind to tissue receptors, inducing vasodilation, bronchoconstriction, and cardiac rate disturbances, which result in the clinical spectrum of an allergic–anaphylactic reaction [15, 18]. Mediator release can be inhibited in mouse bone marrow-derived mast cells (BMMCs) sensitized with specific IgE against antigens such as dinitrophenyl (DNP) or ovalbumin (OVA) by stepwise administration of increasing doses of the antigen at fixed time intervals in a process of desensitization. Compared with non-desensitized BMMCs, desensitized BMMCs, which receive the total antigen dose in a single administration, show a marked reduction in the release of preformed mediators (beta-hexosaminidase and TNF-α) and newly synthesized mediators. Synthesis of leukotrienes LTC4 and LTB4 is inhibited, as is the production of 12(S)-hydroxyheptadeca-5Z, 8E, 10E-trienoic acid (12-HHT), a prostaglandin product. Newly synthesized cytokines, such as IL-6, are also significantly reduced [15].

Table 1 Example of a 3-bag, 12-step BWH/DFCI (Brigham and Women's Hospital in collaboration with the Dana Farber Cancer Institute) desensitization protocol for rituximab

12-step desensitization protocol for rituximab (target dose 500 mg, target infusion solution 2 mg/mL)

Solution 1: 250 mL (0.02 mg/mL), 5 mg per bag

Solution 2: 250 mL (0.2 mg/mL), 50 mg per bag

Solution 3: 250 mL (1.984 mg/mL), 496.07 mg per bag

Step number	Solution number	Drug dilution	Rate of infusion (mL/h)	Time (min)	Amount infused per step (mg)	Cumulative dose infused (mg)
1	1	1/100	2	15	0.010	0.010
2	1	1/100	5	15	0.025	0.035
3	1	1/100	10	15	0.050	0.085
4	1	1/100	20	15	0.100	0.185
5	2	1/10	5	15	0.250	0.435
6	2	1/10	10	15	0.500	0.935
7	2	1/10	20	15	1.000	1.935
8	2	1/10	40	15	2.000	3.935
9	3	1	10	15	4.9607	8.8957
10	3	1	20	15	9.9213	18.8170
11	3	1	40	15	19.8426	38.6596
12	3	1	80	174.375	461.3405	500.0000

Total time of infusion: 339 min = 5.66 h

Table 2 Example of a 4-bag, 16-step BWH/DFCI (Brigham and Women's Hospital in collaboration with the Dana Farber Cancer Institute) desensitization protocol for paclitaxel

16-step desensitization protocol for paclitaxel (target dose 200 mg, target infusion solution 0.8 mg/mL)

Solution 1: 250 mL (0.0008 mg/mL), 0.1 mg per bag

Solution 2: 250 mL (0.008 mg/mL), 2 mg per bag

Solution 3: 250 mL (0.08 mg/mL), 20 mg per bag

Solution 4: 250 mL (0.794 mg/mL), 198.42 mg per bag

Step number	Solution number	Drug dilution	Rate of infusion (mL/h)	Time (min)	Amount infused per step (mg)	Cumulative dose infused (mg)
1	1	1/1,000	2.5	15	0.0005	0.0005
2	1	1/1,000	5.0	15	0.001	0.0015
3	1	1/1,000	10	15	0.002	0.0035
4	1	1/1,000	20	15	0.004	0.0075
5	2	1/100	2.5	15	0.005	0.0125
6	2	1/100	5.0	15	0.01	0.0225
7	2	1/100	10	15	0.02	0.0425
8	2	1/100	20	15	0.04	0.0825
9	3	1/10	5	15	0.1	0.1825
10	3	1/10	10	15	0.2	0.3825
11	3	1/10	20	15	0.4	0.7825
12	3	1/10	40	15	0.8	1.5825
13	4	1	10	15	1.984	3.563
14	4	1	20	15	3.968	7.531
15	4	1	40	15	7.937	15.468
16	4	1	80.0	174.375	184.532	200.000

Total time of infusion: 399 min = 6.66 h

In contrast to activation, which depends on calcium entry into the cell and induces internalization of the antigen–IgE–FcεRI complexes, antigen-IgE complexes remain on the MC surface during desensitization and calcium flux is blunted [15]. In desensitized human basophils, spleen tyrosine kinase (syk) availability is decreased, and this mechanism may play a role in in vitro subthreshold desensitization [19–22]. Finally, signal transducer and activator of transcription (Stat)-6 has been shown to be necessary for desensitization of mast cells in vitro [23]. The profound inhibition of mast cell and basophil mediator release during in vitro antigen desensitization correlates with the protection against anaphylaxis during RDD in patients.

4 Hypersensitivity Reactions to Monoclonal Antibodies and Chemotherapy

4.1 Monoclonal Antibodies

Recombinant monoclonal antibodies currently in use for the treatment of cancer and autoimmune diseases have been described as producing a wide array of infusion reactions—particularly the first monoclonal antibodies, which were fully murine [12, 24]. Since then, antibody engineering has enabled the development of chimeric antibodies, which are 70 % human and 30 % murine (…ximab), "humanized" antibodies (…zumab) with only 5–10 % murine origin, and fully human (…mumab) antibodies with an ever decreasing immunogenic potential [24, 25].

Most HSRs to monoclonal antibodies occur during the first or second infusions, and their clinical presentation can vary from mild cutaneous pruritus to severe anaphylaxis [12, 26, 27]. Also, a cytokine release syndrome presenting with fever has been associated with their use [28]. Some of the most commonly described monoclonal antibodies inducing HSRs are infliximab, rituximab, trastuzumab, and cetuximab.

4.2 Infliximab

Infliximab is a chimeric anti-TNF-α blocking agent, which has proved to be a breakthrough in the treatment of inflammatory arthritides, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and inflammatory bowel disease [29, 30]. Acute HSRs have been reported to occur in 3–5 % of infliximab treatments, within the first 24 h of the infusion—typically between 10 min and 4 h—and their presentation may vary from mild urticaria to anaphylaxis [31]. When these HSRs are severe, it often results in switching to a different TNF-α antagonist (such as etanercept or adalimumab, to which there may also be HSRs) or even back to a less effective oral therapy [31]. A subset of HSRs to infliximab is likely the result of an IgE-mediated mechanism, as documented by the presence of a positive skin test to the drug, and can be successfully desensitized; these reactions usually occur after several infusions of the drug allowing sensitization [12]. Delayed reactions, which occur between 24 h and 14 days after administration, are also observed but are less common (<1 %). There are reports of maculopapular rashes (usually T-cell–mediated), arthralgias, fever, and malaise corresponding to "serum sickness-like" or "eczema-like" reactions. Most delayed reactions are treated with corticosteroids and have good a prognosis [31].

4.3 Trastuzumab

Trastuzumab is a recombinant humanized monoclonal antibody, which recognizes the extra-cellular domain of the human epidermal growth factor receptor (HER)-2 and is used for HER2-over-expressing breast cancer [24]. Severe HSRs have been reported in 0.25 % of patients treated with this monoclonal antibody [27]. Re-challenge with premedication (antihistamines and/or corticosteroids) is possible in some patients, but the majority of them will have to discontinue the treatment, unless desensitization is proposed. As with infliximab, positive skin tests have been found in patients with HSRs to trastuzumab, and reactions usually develop after multiple uneventful infusions of the drug, arguing for an IgE-mediated mechanism [12].

4.4 Rituximab

Rituximab is a chimeric murine/human monoclonal antibody directed against CD20, found on the surface of mature normal and malignant B-lymphocytes. Initially approved for the treatment of refractory or relapsed B-cell lymphomas, it is now also used to treat RA and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and its efficacy has been described for other diseases such as immune thrombocytopenic purpura (ITP) and polymyositis [32–36]. Rituximab can induce various types of HSRs, ranging from a cytokine release syndrome (particularly in the context of a large tumor burden due to massive B lymphocyte lysis) to IgE-mediated reactions. Patients can present with dyspnea, bronchospasm, hypoxia, fever, chills, tremor, urticaria, and angioedema. These reactions tend to be more frequent during the first infusion, affecting more than 50 % of cancer patients in early studies, with a decrease in frequency during subsequent infusions, in parallel with the decrease of the tumor mass [37]. Severe reactions are less frequent, affecting fewer than 10 % of patients, and may be indicative of an IgE-

mediated HSR, in which case the drug should be re-introduced through RDD [12, 38]. In one study, six out of nine patients with a suspected IgE-mediated HSR to rituximab had a positive skin test [12]. In contrast to infliximab and trastuzumab, most of these reactions occur during the first or second exposure to the drug [12].

4.5 Cetuximab

Cetuximab is a chimeric mouse–human (30:70) IgG1 monoclonal antibody, which competitively inhibits the binding of epidermal growth factor (EGFR) and is used for the treatment of tumors that over-express EGFR, such as colorectal cancer, non-small-cell lung cancer, and some epidermoid carcinomas of the head and neck. Although skin toxicity (acneiform rash) is the most common cutaneous adverse reaction, acute infusional HSRs to cetuximab can occur in 25 % of patients, 3–4 % being moderate to severe [39]. Anaphylactic reactions during the first infusion of cetuximab have been described with increased frequency in certain regions of the USA. This intriguing observation led to the discovery that preformed IgE antibodies to the galactose-alpha-1, 3-galactose portion of the cetuximab molecule were responsible for those reactions [40].

In general, HSRs to monoclonal antibodies should be managed as for chemotherapeutic agents. Patients must be clinically assessed for risk stratification. When an allergic reaction is suspected, a skin testing work-up should be performed: for the skin prick test, the full-strength concentration should be used, and if negative, intra-dermal testing with 1:100 and 1:10 dilutions of the drug should follow [12]. When evaluating severe HSRs to cetuximab in particular, skin testing is crucial, and the concentration of specific IgE to cetuximab should be determined [40].

4.6 Chemotherapeutic Agents

Most reports on allergic or anaphylactic reactions to chemotherapy involve platinum drugs, taxanes, doxorubicin, asparaginase, and epipodophyllotoxins, which are discussed in the following sections [11, 41–45]. Although there is an overlap between the clinical manifestations of HSRs induced by the different chemotherapeutic agents, there are also some specific features. The most frequent manifestations in almost all patients with HSRs to chemotherapy are (in order of frequency) cutaneous, cardiovascular, and respiratory [11].

4.7 Platinum Drugs

Platinum drugs are part of the treatment regimen of many types of cancer. In ovarian cancer, carboplatin and cisplatin are extensively used for primary and recurrent disease, which has led to a high prevalence of HSRs to those drugs in that population [46]. HSRs to carboplatin occur in an estimated 2 % of the cancer patient population, whereas the prevalence in ovarian cancer patients is around 16 % and rises to 27 % in patients receiving more than seven cycles of the drug [47, 48]. HSRs to oxaliplatin, which is approved for metastatic colon cancer, were originally considered less common, but with the growing use of this drug in recent years, it has been found that mild and severe reactions occur at frequencies as high as 63 % and 37 %, respectively [49]. The clinical presentation may include flushing, rashes, itchy palms, gastrointestinal symptoms (as nausea, vomiting, diarrhea, or abdominal cramping), hypotension, and tachycardia, usually during the infusion.

Hypersensitivity reactions to platinum drugs are generally consistent with immediate, IgE-mediated HSRs [50, 51]. Sensitization usually develops after repeated intermittent exposure to the drug, as is often the case in patients with ovarian cancer. These patients undergo first line curative/adjuvant treatment, consisting of six cycles of carboplatin and paclitaxel, after which they may enter clinical remission [47]. In contrast to taxanes, in which a great reduction in HSR incidence was seen after implementing premedication with antihistamines and corticosteroids, this strategy is ineffective for HSRs to platinum drugs, as reactions recur in approximately 50 % of the patients, and fatalities have been reported [52–54].

After characterizing the initial reaction regarding timing and severity, patients should undergo skin testing. For skin prick testing, carboplatin 10 mg/mL, oxaliplatin 5 mg/mL, and cisplatin 1 mg/mL are used. If the result is negative, intra-dermal testing should be performed with carboplatin 1 and 10 mg/mL, cisplatin 0.1 and 1 mg/mL, and oxaliplatin (0.5 and 5 mg/mL) [11]. Some authors advocate that skin testing prior to the seventh cycle of carboplatin can identify patients who will develop HSRs, potentially preventing their occurrence [55]. However, because of its impracticality, pre-emptive skin testing is not widely used. Cross-reactivity between platinum drugs has been documented and averages 25 % between cisplatin and carboplatin [56]. Skin testing has been shown to be a useful tool to identify sensitization, and therefore it should be considered when switching to another platinum agent [57].

4.8 Taxanes

Taxanes, such as paclitaxel and docetaxel, are widely prescribed in breast, gynecological, and lung malignancies [46, 58, 59]. Paclitaxel is a cytotoxic compound originally derived from the bark of the North American Pacific yew tree (*Taxus brevifolia*), and docetaxel is a semi-synthetic compound produced from 10-deacetylbaccatin-III, which is found in the needles of the European yew tree (*Taxus baccata*) [60, 61].

Because of their poor solubility, paclitaxel has to be compounded with Cremophor EL and docetaxel has to be compounded with polysorbate-80 [62]. Until the 1990s, a high rate of HSRs was seen during taxane infusion. This decreased to less than 10 % once premedication with H1 and H2 antihistamines and systemic corticosteroids became part of oncology protocols [61, 63–65]. As for platinum drugs, the clinical presentation of HSRs can vary from a mild cutaneous rash to severe anaphylaxis or even death.

IgE-mediated reactions require sensitization by previous exposure, but HSRs to both paclitaxel and docetaxel tend to occur within the first or second exposure, suggesting that the mechanism causing mast cell activation is non-IgE mediated. Cremophor EL and polysorbate-80 have been shown to cause histamine release from mast cells and basophils through complement activation [66]. Interestingly, up to 90 % of patients who have had an HSR to paclitaxel react to docetaxel [67]. This cross-reactivity contradicts the hypothesis of the solvent Cremophor EL being the only trigger of hypersensitivity, and suggests the presence of an allergenic epitope shared by the two drugs. In this regard, a recent report has documented an IgE-mediated reaction to paclitaxel [68]. The clinical presentation of HSRs to taxanes is similar to that seen with platinum drugs, but there are symptoms and signs more frequently associated with this class of drugs—particularly flushing, chest pain with or without dyspnea, and intense back or chest pain [11]. Rapid desensitization protocols have been used with success in patients with HSRs to taxanes [11, 41, 42].

4.9 Doxorubicin

Anthracyclines (doxorubicin hydrochloride and pegylated liposomal doxorubicin) are chemotherapeutic agents isolated from *Streptomyces peucetius* cultures, indicated for the treatment of hematologic and solid cancers (breast) [69]. Doxorubicin is known to cause myelosuppression and cardiotoxicity [69]. The introduction of the liposomal formulation has allowed patients to tolerate higher doses of the drug, with less neutropenia and cardiotoxicity, but HSRs have increased from 0.6–3 % with doxorubicin hydrochloride to 9 % with the liposomal doxorubicin [69]. These therapeutic liposomes activate complement, which might explain the higher rates of HSRs [70].

Most HSRs occur in the first or second infusions and are attributed to sudden activation of the complement by the liposomes. HSRs usually present with a cutaneous rash, but respiratory and cardio-vascular symptoms are also often present [69, 70]. Pegylated liposomal doxorubicin frequently induces palmoplantar erythrodysesthesia syndrome, which is dose related and should not be confused with hypersensitivity [71]. Anthracyclines are vesicants and should not be used for skin testing.

4.10 L-Asparaginase

L-asparaginase is a bacterial enzyme available in three different formulations (native and pegylated forms derived from *Escherichia coli*, and a native form derived from *Erwinia chrysanthemi*) and is used for treating acute lymphoblastic leukemia [44, 72]. It is a highly immunogenic product, against which antibodies (IgG and IgE), which are thought to cause HSRs, are rapidly formed [73]. By binding to asparaginase, those antibodies render it inactive, thereby causing a marked reduction in its potency [74]. HSRs range from local reactions at the site of injection to anaphylaxis, and can affect up to 60 % of patients, although the rate appears to be significantly lower with the pegylated form, given its lower immunogenicity [72]. The *E. chrysanthemi* form appears to rarely cross-react with the *E. coli* form, allowing substitution from one to the other [74]. Given this high HSR rate, close monitoring—and the ability to treat anaphylaxis promptly—are necessary when administering asparaginase. Desensitization protocols have been used to successfully re-administer asparaginase after a severe HSR [75].

4.11 Epipodophyllotoxins (Teniposide/Etoposide)

Teniposide is used for the treatment of acute lymphoblastic leukemia and etoposide is used for refractory testicular tumors, small-cell lung cancer, and ovarian cancer. Cremophor EL (teniposide) and polysorbate-80 (etoposide) are considered responsible for HSRs to epipodophyllotoxins, as in the case of taxanes [76, 77]. An oral formulation of etoposide (etoposide phosphate), without polysorbate-80, is usually well tolerated, although cases of HSRs have also been reported [78, 79]. Premedication and a slow infusion rate may reduce the risk of HSRs on re-challenge with epipodophyllotoxins, but patients with severe reactions should undergo desensitization.

Table 3 provides a brief overview of the different clinical presentations of HSRs to the most commonly encountered drugs.

4.11.1 Desensitization Protocols: Eligibility, Safety, and Efficacy

The Brigham and Women's Hospital in collaboration with the Dana Farber Cancer Institute (BWH/DFCI) have developed standardized RDD protocols applicable to many chemotherapeutic agents and monoclonal antibodies, with a remarkable record regarding safety and efficacy [11, 12, 41–43]. RDD is performed only in patients for whom no alternative drug can adequately replace the one that caused the HSR. Type I HSRs and cytokine release symptoms can be successfully prevented by RDD, in contrast to severe

delayed reactions, which are contra-indications to the procedure (Fig. 1) [11, 12]. In some instances, a non-severe delayed maculopapular rash can be the prelude to a severe type I HSR and hence may warrant RDD [80]. Skin testing is a useful tool to predict the risk of reaction upon re-exposure and, if positive, the drug should only be re-administered through RDD [11, 12]. However, caution has to be exercised when drawing conclusions from a negative skin test. The negative predictive value (NPV) of platinum drug skin testing appears to be quite high, and anaphylaxis has never been reported following a negative skin test [11, 55]. In contrast, few data exist on the NPV of skin testing with monoclonal antibodies, and it is prudent to desensitize patients with a moderate or severe HSR despite a negative skin test [12]. Skin testing could be a useful tool to identify patients with IgE-mediated reactions to taxanes in the near future, although this approach still needs to be validated [14, 68].

RDD is performed under the direct supervision of an allergist with expertise in desensitization, and with a 1:1 nursing ratio. Nurses are specifically trained to perform those procedures, as they must be able to promptly recognize and adequately treat any breakthrough reactions. Patients are also advised to report any symptom they may experience during RDD. The severity of the initial reaction and the co-morbidities of the patient dictate the choice of protocol and the set-up for RDD [an intensive care unit (ICU) versus an outpatient infusion center]. In patients with a severe initial reaction (i.e. a drop in blood pressure or oxygen saturation; grade 3 reaction) the first desensitization is performed in the ICU, after which—if no severe reaction occurs during the procedure—subsequent desensitizations can be performed in an outpatient infusion center. Similarly, patients with heart or pulmonary disorders that significantly reduce their capacity to tolerate a breakthrough reaction are first desensitized in the ICU. The most commonly used protocol for RDD consists of 3 bags of increasing concentrations of the drug, and is infused over 12 steps, where the rate of the infusion is gradually increased (Table 1). For patients with an initial severe HSR or with significant co-morbidities, a 4-bag, 16-step protocol can be used (Table 2). Importantly, beta-blockers are withheld for at least 24 h before desensitization, as they interfere with epinephrine, the cornerstone for the treatment of anaphylaxis [6].

In a cohort of 98 patients who had suffered 101 HSRs (most of them to carboplatin or paclitaxel), 413 desensitizations were performed with the aforementioned protocol. During these desensitizations, no reaction was elicited in 67 %, while 27 % presented a mild reaction and 6 % presented a severe reaction [11]. However, all reactions were milder than the initial HSR and, after a pause in the infusion and the appropriate treatment, every patient was able to complete the desensitization protocol [11]. Notably, epinephrine had to be used in only one case. Also, most reactions occurred during the first and second desensitization procedures and steadily decreased afterwards [11].

In another cohort study, 23 patients underwent RDD with monoclonal antibodies (infliximab, trastuzumab, and rituximab) according to the same protocol [12]. Only two severe reactions occurred during RDD, one of which led the patient to stop the drug and both of which occurred after a first uneventful desensitization, showing the need for continued vigilance at each desensitization [12].

Overall, RDD has been performed successfully with carboplatin, cisplatin, oxaliplatin, paclitaxel, docetaxel, liposomal doxorubicin, uromitexan, rituximab, trastuzumab, and infliximab. Finally, others using similar desensitization protocols have also shown the safety and efficacy of RDD for chemotherapeutic agents [13, 14, 81–83].

4.12 Premedication for Desensitization Protocols

Premedication with histamine (H)-receptor blockers has long been included in most oncological chemotherapy protocols, since this strategy has been shown to decrease the incidence of immediate HSRs in multiple clinical studies, particularly those including taxanes [84]. To minimize breakthrough HSRs during RDD, H1 and H2 blockers are part of every premedication regimen [11, 12, 57]. The choice of a specific antihistamine depends on the pharmacokinetics, safety profile, and availability of each medication. Corticosteroids (dexamethasone) are often given for their anti-emetic properties and have been shown to reduce the rate of HSRs to taxanes when given

Table 3 Frequent presentations of hypersensitivity reactions (HSRs) to different agents

Agents	Number of infusions prior to first reaction	Clinical manifestations of hypersensitivity
Platins	6–8	Rash, pruritus, flushing, respiratory, cardio-vascular
Taxanes	0–1	Cutaneous, pain (lumbar)
Biological agents	0–1 or >5	Fever, chills, rash, respiratory, cardio-vascular

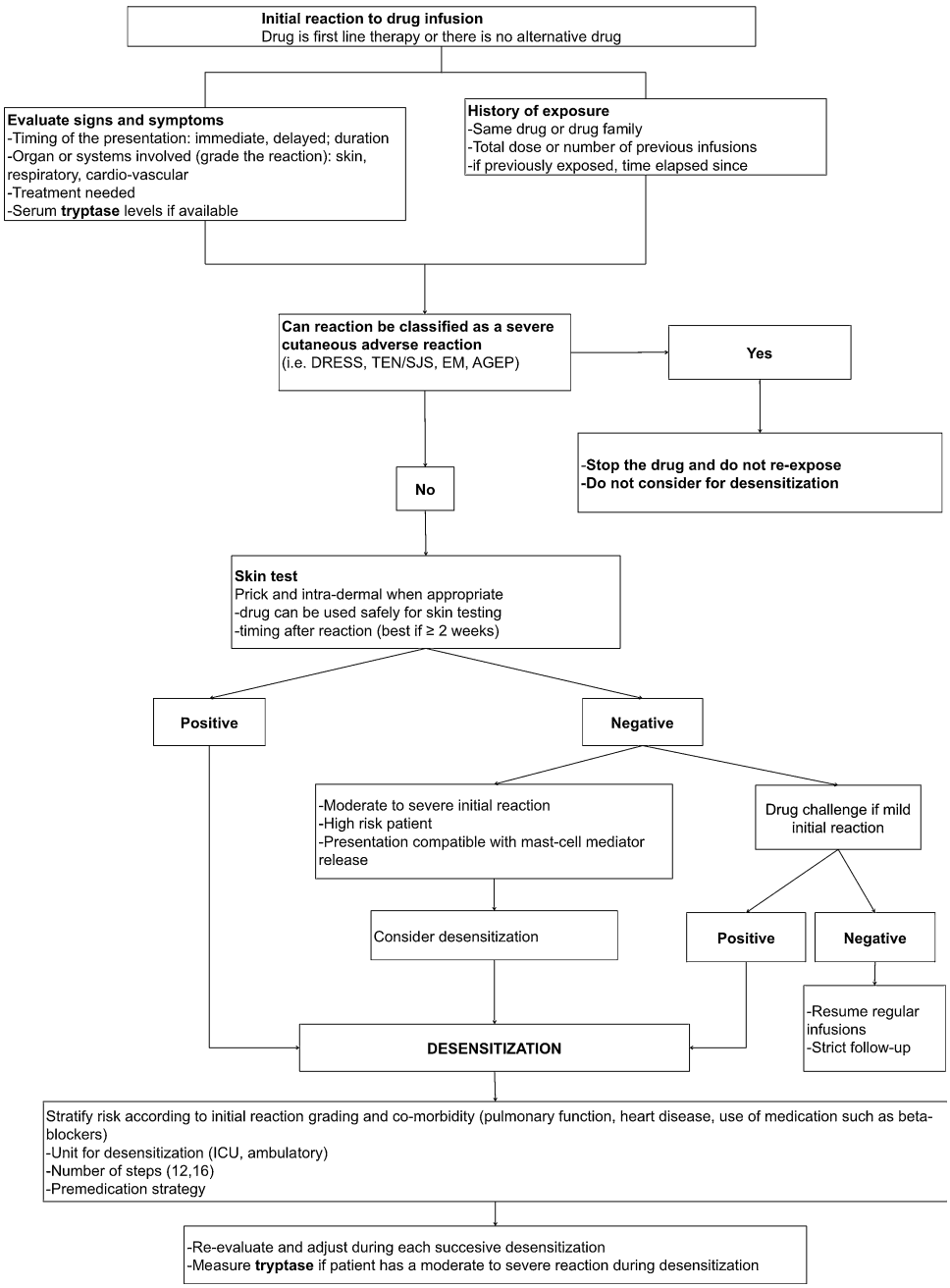

Fig. 1 Approach to patients with a hypersensitivity reaction to monoclonal antibodies or chemotherapy. *AGEP* acute generalized exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *EM* erythema multiforme, *ICU* intensive care unit, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

in association with antihistamines [85]. In addition, they can prevent the fluid retention associated with docetaxel [86]. Premedication regimens should also be adjusted to the initial presentation or to breakthrough reactions, which might still occur during RDD. The use of acetylsalicylic acid to block prostaglandins and montelukast to block cysteninyl leukotriene receptor 1 has demonstrated efficacy in the management of HSRs in patients presenting with flushing and respiratory symptoms, respectively, especially when platinum drugs are concerned [87].

5 Conclusion

Rapid drug desensitization has proven to be a safe and effective way of administering first line therapy to patients with HSRs to chemotherapy drugs and monoclonal antibodies. RDD protocols should be administered only by highly trained allergists and nurses who have experience in determining which reactions are amenable to desensitization, and can identify high risk patients and provide them with appropriate care. In recent years, the availability of new anti-neoplastic drugs and therapeutic monoclonal

antibodies has increased the potential for HSRs. Development of desensitization protocols for these new medications requires careful assessment of the potential risks and benefits. RDD provides an extremely powerful treatment modality for patients with HSRs to drugs for which alternatives are deemed unsatisfactory. Efforts should be made to increase awareness of the remarkable safety and efficacy of RDD among non-allergists, especially in the fields of oncology and rheumatology, so as to favor its universal application. Development of desensitization units to provide state-of-the-art care is possible only through coordinated teamwork.

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