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Diagnoses and Management of Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: Reactions to Taxanes and Monoclonal Antibodies

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Abstract Due to the increase in utilization of chemotherapies and antibodies, drug hypersensitivity reactions have increased dramatically worldwide, preventing the use of first-line therapies and impacting patients' survival and quality of life. Some of the more frequently used medications in cancer include taxanes for ovarian, lung, breast, and prostate cancers. Monoclonal antibodies are used in the treatment of neoplastic, autoimmune, and inflammatory diseases, and their clinical applications are becoming broader. Monoclonal antibody targets include CD20, HER-2, EGFR, IL-6 receptor, TNF-α, CD30, VEGF-A, IgE, and more, and examples of immune-mediated and inflammatory diseases that respond to monoclonal antibodies include rheumatoid arthritis, Crohn's disease, ulcerative colitis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, Wegener's granulomatosis, microscopic polyangiitis, ankylosing spondylitis, plaque psoriasis, and asthma. Neoplastic diseases include non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and colorectal, breast, gastric, and lung cancer. The clinical presentation of drug hypersensitivity reactions ranges from mild cutaneous reactions to life-threatening symptoms including anaphylaxis. Rapid drug desensitization (RDD) has become a groundbreaking approach to the management of immediate drug hypersensitivity reactions IgE and non-IgE mediated. It is the only effective procedure that enables sensitized patients to receive the full treatment dose safely, thus representing an important advance in the patients' treatment and prognosis. The aim of this review is to provide an update on hypersensitivity reactions to commonly used monoclonal and taxanes, their clinical presentations, diagnosis, and the use of RDD for their management.

Keywords Taxanes · Monoclonal antibodies · Rapid drug desensitization · Drug hypersensitivity reaction · Adverse drug reaction

Abbreviations

ADR	Adverse drug reaction
DHR	Drug hypersensitivity reactions
HSR	Hypersensitivity reactions
IgE	Immunoglobulin E
mAbs	Monoclonal antibodies
RDD	Rapid drug desensitization

Introduction

Adverse drug reactions are defined by WHO as "any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment" and are estimated to occur in 15 to 30 % of hospitalized patients, with 0.1 % of deaths reported for clinic patients and 0.01 % for surgical patients [1, 2]. The incidence of ADR is 5 % in adult ambulatory patients. Drug hypersensitivity reactions (DHR) correspond to 10 to 15 % of all adverse reactions [1]. In this context, DHR affect more than 7 % of the general population representing an important public health problem [3].

The last international consensus on drug allergy suggests that the term "allergy" to be restricted to the reactions in which it was possible to establish an immunological mechanism,

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either via in vivo or in vitro testing. If is not possible to demonstrate, priority should be given the term "DHR" (Fig. 1) [4].

DHR is an immunologically mediated reaction; they can be an acute as immediate or delayed. Immediate hypersensitivity reaction (HSR) was defined as an adverse reaction during or under 1 h of the infusion and with symptoms suggestive of mast cell/basophil degranulation, although in patient with premedications, the reactions can be delayed to more than 1 h. The definition of delayed HSR is an adverse reaction with onset of greater than 1 h to 1 week after the infusion and with symptoms suggestive of either a cell-mediated HSR (e.g., a maculopapular rash) or a mast cell/basophil-mediated HSR (e.g., flushing with onset <48 h after the infusion). The severity of immediate HSR was graded by Brown, as described in Table 1 [5–7].

Some patients can experience reactions such as chills, fever, nausea, and malaise. These symptoms have been attributed to the release of proinflammatory cytokines, interleukin-6 and TNF-α, also known as cytokine storm [8].

Patients with chronic inflammatory and cancer diseases are increasingly exposed to new monoclonal antibodies (mAbs) and chemotherapy drugs, respectively, with sensitization potential. In the last 15–20 years, clinical and basic research has provided evidence that patients with type I and type IV reactions can be safely reexposed to their allergy through desensitization protocols (Table 2) [8].

The aim of this review is to provide up to date information on the presentation, diagnoses, and management of HSR to taxane chemotherapy agents and biological agents including drug challenges and desensitization protocols.

Taxanes

In the USA, the third leading cause of fatal drug-induced anaphylaxis is antineoplastics [9], and among the most frequently implicated antineoplastics in these reactions are taxanes. Since their commercialization, the US Food and Drug Administration reported more than 300 fatalities [10–12].

In gynecology, taxanes are an integral part of the chemotherapy regimen used for lung, breast, and prostate cancers [13, 14].

Paclitaxel and docetaxel are the two main taxane molecules, and recently cabacitaxel and Abraxane (albumin-bound paclitaxel) have been added to the taxane family. Paclitaxel is a natural molecule that was originally isolated from the bark of the Pacific yew tree, and docetaxel is a semi-synthetic molecule derived from a taxoid precursor found in European yew tree needles. Cremophor is used to solubilize paclitaxel molecules, and polysorbate is used to solubilize 80 for docetaxel. These solvents can cause complement activation leading to anaphylatoxin production and mast cell activation [15].

In the initial studies with taxanes, DHR were very frequent and led to the use of premedication with antihistamine and corticosteroids. HSR occur in almost 10 % of patients and in 1 % are severe [16, 17]. Reactions occur during the patient's first or second lifetime drug exposure in up to 40 % of the patients and include symptoms such as throat tightness, flushing, hypotension, and dyspnea. However, the same patients also report atypical symptoms such as severe chest and back and/or pelvic pain [12, 17].

Patients with severe cutaneous adverse drug reactions (e.g., blistering skin reactions/Stevens-Johnson syndrome/desquamative) are advised to avoid all taxanes.

Diagnosis of Taxane Hypersensitivity Reactions

Immunoglobulin E (IgE)-mediated HSR to the taxane molecule has been reported, generating interest in providing skin test evaluations for patients with DHR to taxanes [18, 19].

Brigham and Women's Hospital (BWH) Drug Hypersensitivity and Desensitization Center and Dana-Farber Cancer Institute (DFCI) conducted a study with 164 patients treated for a taxane-related HSR from April 2011 to

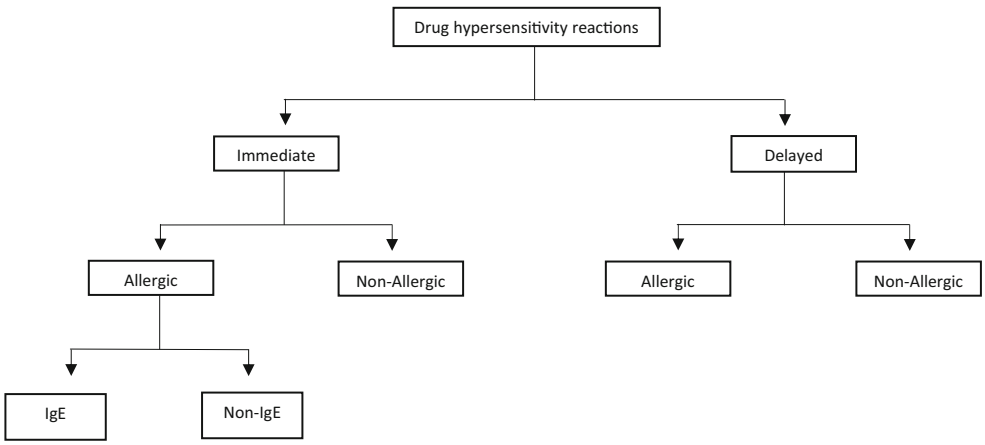

Fig. 1 Classification of drug hypersensitivity reactions (DHRs)

Table 1 Severity grading system of immediate hypersensitivity reactions [adapted from Brown [6]]

Grade	Severity	Description
1	Mild	Symptoms are limited to the skin (e.g., flushing) or involve a single organ/system and are mild (e.g., mild back pain)
2	Moderate	Symptoms involve at least 2 organs/systems (e.g., flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation
3	Severe	Symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic ≤90 mmHg and/or syncope) and/or oxygen saturation (≤92 %)

August 2014, the largest cohort of patients treated for taxane-induced HSR reported to date. Skin testing was performed in 145 patients: 103 (71 %) had positive results, 35 (24 %) had negative results, 6 (4 %) had equivocal results, and 1 (0.7 %) had results that converted from negative to positive [20].

Of 138 patients desensitized, 29 (21 %) had an immediate and 20 (14 %) had a delayed HSR with the procedure. Forty-nine patients were challenged, two (4 %) had a mild immediate HSR, and one (2 %) had a delayed HSR. Factors associated with an HSR during challenge were ovarian, fallopian, or peritoneal cancer and atopy (allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or hymenoptera allergy) for immediate reactions, and for the delayed reactions, older age is the factor associated (Table 3). No patients had a severe immediate HSR with desensitization or challenge. Thirty-six (22 %) patients eventually resumed regular infusions. These patients were more likely to have negative skin test responses and to have experienced a delayed or mild immediate initial HSR [20].

This study showed that risk stratification based on skin testing and the severity of the initial HSR can safely guide DHR management and allow a significant number of patients to resume regular infusions (Fig. 2) [20].

Rapid Drug Desensitization to Taxanes

The DFCI/BWH Desensitization Program has generated a flexible 12-to-20 step protocol, which rendered mast cells unresponsive by delivering ×2 to ×2.5 doses of drug antigens at fixed time intervals starting at 1/1000 to 1/100 dilutions of the final concentration [12]. The challenge of rapid drug desensitization (RDD) is to gradually increase the dose of medication without reaching a threshold concentration that would trigger anaphylaxis, although mast cells/basophils may release some amount of mediators during RDD. Figure 3 illustrates the concept that each administered dose induces more cell inhibition and raises the threshold for clinical symptoms.

Patients with HSR grade I and II and skin test positive or grade II and skin test negative with comorbidities are desensitized with 12 steps (3 bags). An example of 12-step RDD for taxane is described in Table 4. Patients with HSR grade III or with comorbidities (e.g., uncontrolled asthma and/or significant impairment in FEV1, unstable or symptomatic coronary heart disease, and poor Eastern Cooperative Oncology Group performance status), beta-blocker users, or pregnant are indicated to follow a 16–20-step protocol on intensive care unit (Table 5) [8].

In one study where 77 desensitizations to paclitaxel and docetaxel in 17 patients were performed, 72 were without reactions. During the desensitization protocol, four patients had symptoms, such as palmar erythema, pruritus, mild abdominal pain, chest burning sensation, and mild flushing. All four patients successfully completed the planned infusions in their entirety. Three of the four patients had subsequent desensitizations without HSR. The fourth patient no longer received taxane because she opted to change therapeutic agent [21].

RDD is a safe and effective method of reintroducing taxanes in patients with past immediate HSR [12, 21, 22]. Yet this method is time-consuming and necessitates a 1:1 nursing ratio [10].

Table 2 Indications and contraindications of rapid drug desensitization [modified from Giavina-Bianchi [8]]

Indications	High-risk patients	Contraindications
Reaction type I (mast cells/IgE/basophils) Reaction type IV (except SCARs)	Severe anaphylaxis (intubation)	Severe cutaneous adverse reactions (SCARs, SJS/TEN, DIHS/DRESS, AGEP)
No alternative drug	Severe respiratory disease	Immunocytotoxic reactions (type II reactions)
Drug is more effective and/or associated with less side effects	Severe cardiac disease	Vasculitis
Drug has a unique mechanism of action	Severe systemic diseases	Serum sickness-like (type III reactions)
	Use of beta-blockers, ACE inhibitors, pregnancy	

SJS Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *DIHS* drug-induced hypersensitivity syndrome, *DRESS* drug reaction (rash) with eosinophilia and systemic symptoms, *AGEP* acute generalized exanthematous

Table 3 Factors associated with hypersensitivity reactions to taxane desensitization or challenge [adapted from Picard et al. [20]]

Outcomes and contributing factors	Type of reaction	*P* value
Older patient[b]	Immediate HSR[a]	0.8
	Delayed HSR[a]	0.02
Atopy[c]	Immediate HSR[a]	0.001
	Delayed HSR[a]	0.7
Ovarian, fallopian, peritoneal cancer[d]	Immediate HSR[a]	0.1
	Delayed HSR[a]	0.007
Negative skin test response[e]	Immediate HSR[a]	0.2
	Delayed HSR[a]	0.5

[a] Compared with no HSR

[b] Age was included in the model because it increased its accuracy to 70.7 %

[c] Defined as the presence of any of the following: history of allergic asthma and/or rhinoconjunctivitis, food allergy, atopic dermatitis, or hymenoptera allergy (compared with no atopy)

[d] Compared with any other type of cancer

[e] Compared with any other skin test outcome (positive, equivocal, or not done)

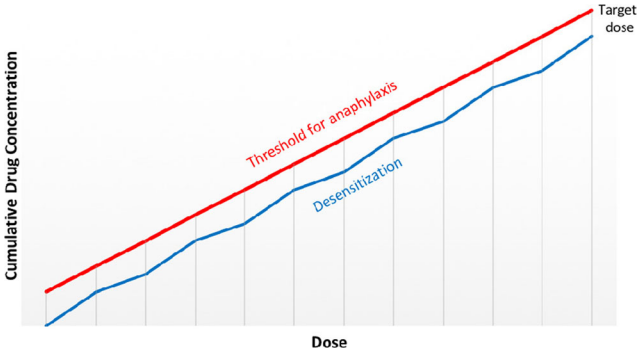

Fig. 3 Putative mechanism of rapid drug desensitization

Monoclonal Antibodies

The applications of mAb drugs cover a wide range of diseases, such as the treatment of neoplastic, inflammatory, and autoimmune diseases [23, 24]. This drug class started in the 1970s, but mAb use became widespread in the past decade, leading to an increase in reported DHR and sometimes preventing the

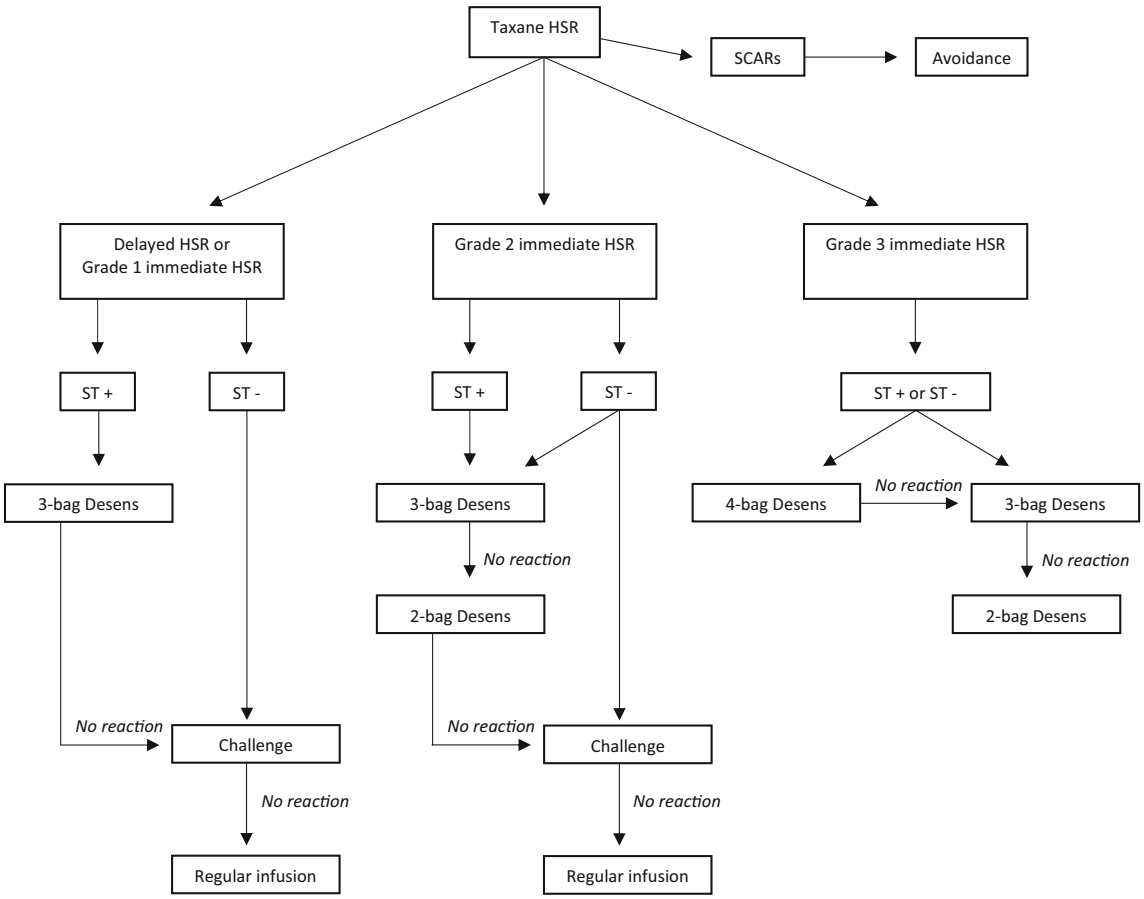

Fig. 2 Algorithm to taxane reintroduction in patients with HSR. In patients with an HSR with desensitization or challenge, premedication is generally adjusted for the next procedure, which is administered by using either the same or a longer protocol. Patients in whom the HSR does not recur are then treated with a shorter desensitization protocol, challenge, or regular infusion, according to the algorithm. See Table 1 for a description of the grading of immediate HSR. Severe cutaneous adverse drug reactions (*SCARs*) include Stevens-Johnson syndrome and desquamative/blistering skin reactions. [Adapted from Picard [20]]

Table 4 Example of 12-step protocol to paclitaxel

Nome of medication			Taxane			
Target dose (mg)			300			
Standard volume per bag (ml)			250			
Final rate of infusion (ml/h)			80			
Calculated target concentration (mg/ml)			1.2			
Standard time of infusion (minutes)			187.5			
	Volume		Concentration (mg/ml)		Total mg per bag	Amount infused (ml)
Solution 1	250	ml of	0.012	mg/ml	3	9.38
Solution 2	250	ml of	0.120	mg/ml	30	18.75
Solution 3	250	ml of	1.190	mg/ml	297.638	250
Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.5	15	0.63	0.0075	0.0075
2	1	5	15	1.25	0.015	0.0225
3	1	10	15	2.5	0.03	0.0525
4	1	20	15	5	0.06	0.1125
5	2	5	15	1.25	0.15	0.2625
6	2	10	15	2.5	0.3	0.5625
7	2	20	15	5	0.6	1.1625
8	2	40	15	10	1.2	2.3625
9	3	10	15	2.5	2.9764	5.3389
10	3	20	15	5	5.9528	11.2916
11	3	40	15	10	11.9055	23.1971
12	3	80	174.375	232.5	276.8029	300

The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are not completely infused. Total time = 5.66 h

use of first-line therapies. Some of the most frequently used mAbs are presented in Table 6, including their targets, incidence of overall injection/infusion site reactions, and severe immediate HSR.

MAb immunogenicity depends on the presence of human content, varying from chimeric mouse-human, humanized, to a fully human mAb [25]. Even with fully human mAbs, such as adalimumab and ofatumumab, severe DHR can occur. First exposure to mAbs can lead to DHR, as it can be observed with cetuximab and trastuzumab, predominantly in the first three infusions, as with omalizumab, or after multiple exposures [23, 24].

In a significant number of patients, infusion-related reactions to mAbs can occur. Certain patients can manifest with nausea, chills, fever, and malaise [7, 25, 26]. For trastuzumab, typical first-time infusion reactions include chills and/or fever and occur in approximately 40 % of patients [27]. These are thought to be due to the release of proinflammatory cytokines (such as IL-6 and TNF-α) and do not tend to be severe, except for the findings of the

Table 5 Risk and benefits to rapid drug desensitization [adapted from Giavina-Bianchi [8]]

Risk grade	Features	Protocol/time	Infusion center
Low risk	DRH grades 1–2	12 steps 5.6 h	Outpatient
High risk	DHR grade 3	16–20 steps	Intensive care unit
	Severe and/or uncontrolled disease (respiratory FV1 < 1 L, cardiac)	6.6–8 h	
	Beta-blocker		
	Pregnancy		
	Use of morphine/opioid derivatives		

DHR drug hypersensitivity reaction

Table 6 Biological agents: actions, incidence, and hypersensitivity drug reactions [modified from Galvão and Castells [40]]

Drug	Target	Overall reactions	HSR
Rituximab (Rituxan®) IV	CD20	77 % (first infusion) [52]	5–10 % [53]
Ofatumumab (Arzerra®) IV	CD20	44 % (first infusion) [25] 67 % (combination therapy) [54]	2 % [54]
Obinutuzumab (Gazyva®) IV	CD20	66 % [55, 56]	–[a] [57]
Trastuzumab (Herceptin®) IV	HER-2	40 % (mild; first infusion) [58]	0.6–5 % [59]
Cetuximab (Erbitux®) IV	EGFR	15–21 % [60]	1.1–5 % [61–64] 14–27 % (Southern USA) [65–67]
Tocilizumab (Actemra®) IV	IL-6 receptor	7–8 % [68]	0.1–0.7 % [68]
Infliximab (Remicade®) IV	TNF-α	5–18 % [69]	1 %[a] [69]
Etanercept (Enbrel®) SC	TNF-α	15–37 % [70]	<2 % [70]
Adalimumab (Humira®) SC	TNF-α	20 % [71]	1 % [71]
Golimumab (Simponi®) SC	TNF-α	4–20 % [72, 73]	Not reported
Certolizumab (Cimzia®) SC	TNF-α	0.8–4.5 % [74, 75]	Not reported
Brentuximab (Adcetris®) IV	CD30	12 % [33]	–[a] [34–36]
Bevacizumab (Avastin®) IV	VEGF-A	<3 % [76]	Not reported
Omalizumab (Xolair®) SC	IgE	45 % [77]	00.9–0.2 % [77, 78]

[a] Case reports of anaphylaxis

anti-CD28 mAb TGN1412 phase 1 trial in which six volunteers who received the drug developed multiorgan failure as a result of a severe cytokine storm [28].

Grade 2–4 hypersensitivity reactions were reported in 27 % of 51 patients treated with cetuximab in a Florida Veterans Affairs facility [29]. This association was later explained by the role of a galactose-a-1,3-galactose IgE antibodies possibly generated by tick exposure (*Amblyomma americanum*—lone star tick), whose geographical distribution matched that of cases of anaphylaxis to meat and cetuximab hypersensitivity. The carbohydrate galactose-a-1,3-galactose is expressed on nonprimate mammalian proteins and present on the cetuximab heavy chain [30].

Immediate and delayed hypersensitivity reactions (skin lesions with CD4þ T cells and eosinophils infiltrate in the upper dermis) can occur secondary to the use of tocilizumab [31, 32].

Infusion-related reactions tend to occur in approximately 12 % patients, and the most common signs and/or symptoms include chills, nausea, dyspnea, pruritus, pyrexia, and cough. There have been reports on anaphylaxis associated with brentuximab, and desensitizations have been performed [33–36].

In addition, there have been reports of type I, III, and IV DHR related to mAb infusion. Patients can present with signs and symptoms typical of the type I HSR, including cutaneous, cardiovascular, respiratory, gastrointestinal, and/or neurological manifestations, while the drug is being infused or within the first hour after administration. Delayed DHR suggestive of type IV reactions have been reported, as well as reactions suggestive of type III reactions (serum sickness-like), with symptoms such as rash, myalgia, fever, polyarthralgias, pruritus, edema, and fatigue [32, 37]. Examples of the latter are DHR induced by infliximab (1 to 14 days after the infusion) and omalizumab (1 to 5 days after infusion) [38, 39].

mAbs whose application is subcutaneous might elicit injection site reactions. These include local redness, warmth, burning, stinging, itching, urticaria, pain, and induration, varying in frequency from 0.8 to 4.5 % with certolizumab to up to

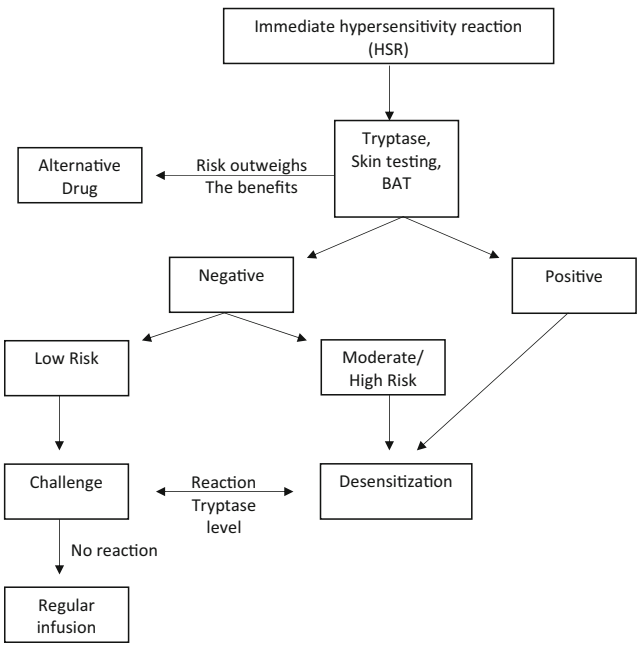

Fig. 4 Propose algorithm for rapid drug desensitization. [Adapted from Giavina-Bianchi [8]]

45 % with omalizumab. Such reactions can start in the first hour of the injection and tend to resolve in the subsequent days [24].

When managing a DHR related to mAb, the infusion must be immediately stopped and it is strongly advised to obtain a tryptase level within 30 to 120 min of the reaction [40–42].

Tryptase is one of many mast cell-derived mediators, and it can be measured in peripheral blood. Rise in serum tryptase during an anaphylactic event may peak 15–60 min after the onset of symptoms and then decline with a half-life of about 2 h. Acute serum total tryptase level should be at least 20 % plus 2 ng/ml over the baseline level (of tryptase) to be indicative of mast cell activation [43].

Increased levels of tryptase will point out to a reaction with an underlying mast cell activation mechanism. Epinephrine is indicated in severe reactions involving hypotension and/or desaturation and should be promptly administered [44].

Diagnosis of Monoclonal Antibody Hypersensitivity Reactions

Skin testing with the offending agent can be done when an IgE-mediated reaction is suspected, but this specific investigation should wait 2 to 4 weeks to minimize the chances of false-negative results [40, 45]. The negative predictive value for most mAbs is not known. It was reported that out of 23 patients desensitized to trastuzumab, infliximab, or tituximab, only 13 patients had positive skin test [7].

If skin tests are negative, tryptase levels obtained during the reaction are within normal range and/or the clinical history is not suggestive of a true, IgE-mediated, allergic reaction, a graded challenge with the medication can be performed [40]. The challenge consists of providing the patient with 1/10 of the total dose of the offending drug under medical surveillance, and if no reactions occur, the patient can receive the rest of the dose. If the challenge is positive, the patient may be a candidate to desensitization; likewise, if the challenge is negative, the patient can resume regular infusions [46, 47].

Rapid Drug Desensitization for Monoclonal Antibodies

RDD is a novel therapeutic option for selected patients who present with DHR to mAbs [48]. The general algorithm for rapid drug desensitization should be applied for mAb HSR (Fig. 4) [8]. A standard desensitization protocol to mAbs has been developed with 3 intravenous dilution bags, 12 steps, and an approximate total duration of 6 h [49]. High-risk patients can be desensitized with additional dilutions and/or steps (16 or 20 steps). It enables the patient to receive the full treatment dose while protecting from anaphylaxis [7].

Patients with type I DHR to mAbs are candidates for RDD, and immediate injection site and systemic reactions elicited by subcutaneous agents (such as adalimumab and etanercept) have also had successful desensitization protocols established (Tables 7, desensitization to adalimumab, and 8, desensitization to ofatumumab) [40, 50]. For mAbs that are administered subcutaneously, a six-step rapid desensitization protocol was developed. The initial dose is typically 1/10 of the target doses of the drug below the threshold of HSR, and the doses are doubled until it reaches the target dose in six steps with an interval of 30 min.

Until now, it has been successfully desensitized mAb HSR to rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab.

Conclusion

Most patients with DHR are candidates for RDD, except for patients with SCARs. The success of rapid drug desensitization relies on categorization of the intensity and nature of the initial reaction, skin testing, and risk stratification, with adjustments based on the patient's response.

Table 7 Subcutaneous desensitization to adalimumab in a 26-year-old woman treated for rheumatoid arthritis and presenting an immediate injection site reaction [adapted from Bavbek et al. [50]]

Step	Concentration (mg/ml)	Time (min)	Cumulative time (min)	Volume administered per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	4	30	30	0.25	1	1
2	4	30	60	0.5	2	3
3	40	30	90	0.1	4	7
4	40	30	120	0.2	8	15
5	40	30	150	0.4	16	31
6	40	30	180	0.6	24	55

Time per step = 30 min; number of steps = 6; total dose = 55 mg

Table 8 Desensitization to ofatumumab in 16 steps: patient, 68-year-old man treated for chronic lymphocytic leukemia who presented a grade 2 reaction to the drug (throat tightness, cough, and angioedema)

Bag	Volume per bag (ml)		Concentration (mg/ml)			Total dose per bag (mg)		Amount of bag infused (ml)
1	250		0.002			0.500		9.38
2	250		0.040			10.000		9.38
3	250		0.400			100.000		18.75
4	250		3.968			992.106		250.00
Step	Bag	Rate (ml/h)	Time (min)	Cumulative time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)	Fold increase per step
1	1	2.5	15	15	0.625	0.001	0.001	2
2	1	5	15	30	1.25	0.003	0.004	2
3	1	10	15	45	2.5	0.005	0.009	2
4	1	20	15	60	5	0.010	0.019	2.5
5	2	2.5	15	75	0.625	0.025	0.044	2
6	2	5	15	90	1.25	0.050	0.094	2
7	2	10	15	105	2.5	0.100	0.194	2
8	2	20	15	120	5	0.200	0.394	2.5
9	3	5	15	135	1.25	0.500	0.894	2
10	3	10	15	150	2.5	1.000	1.894	2
11	3	20	15	165	5	2.000	3.894	2
12	3	40	15	180	10	4.000	7.894	2.485
13	4	10	15	195	2.5	9.921	17.815	2
14	4	20	15	210	5	19.842	37.657	2
15	4	40	15	225	10	39.684	77.341	2
16	4	80	174.375	399.375	232.5	922.659	1000.000	2

The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are not completely infused. Total infusion time = 6.6 h, standard volume per bag = 250 ml, final rate of infusion = 80 ml/h, number of bags = 4, time per step = 15 min, total number of steps = 16, total dose = 1000 mg

The largest desensitization study worldwide reported that 370 highly allergic patients received 2177 successful desensitizations to 15 drugs, 3 of which (bevacizumab, tocilizumab, and gemcitabine) are unprecedented. Most importantly, carboplatin-desensitized patients had a nonstatistically significant lifespan advantage over nonallergic controls, indicating that the efficacy of carboplatin was not reduced in allergic patients and that RDD protocols are as effective as regular infusions [51].

RDD is safe, based on the results of the 2177 desensitizations, and 93 % had no or mild reactions, whereas 7 % had moderate to severe reactions, which did not preclude the completion of the treatment, and there were no deaths (Fig. 5) [51].

Rapid drug desensitization is a groundbreaking procedure for the management of immediate drug hypersensitivity reactions. It protects patients against anaphylaxis, maintaining patients on first-line therapy, thus representing an important advance in patients' treatment and prognosis.

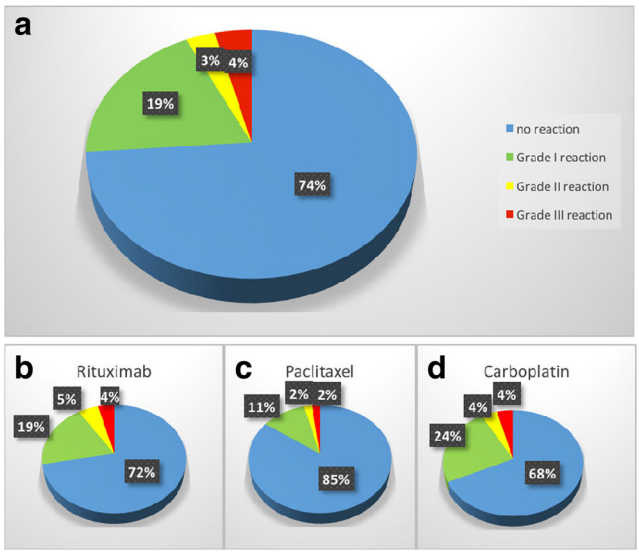

Fig. 5 **a** Percentage and severity of breakthrough reactions occurring during 2177 desensitization courses to chemotherapy and monoclonal. **b** One hundred twenty reactions to rituximab. **c** Five hundred fifty reactions to paclitaxel. **d** One thousand sixty-nine reactions to carboplatin. [Adapted from Sloane [51]

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