



Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: The Role of Desensitizations

Mariana Castells*

Allergy and Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

OPEN ACCESS

Edited by:

Vanesa Esteban,
Instituto de Investigación Sanitaria de
la Fundación Jiménez Díaz, Spain

Reviewed by:

Michael Breitenbach,
University of Salzburg, Austria
Sinisa Savic,
University of Leeds, United Kingdom

*Correspondence:

Mariana Castells
mcastells@bwh.harvard.edu

Specialty section:

This article was submitted to
Inflammation,
a section of the journal
Frontiers in Immunology

Received: 31 May 2017

Accepted: 20 October 2017

Published: 08 November 2017

Citation:

Castells M (2017) Drug
Hypersensitivity and Anaphylaxis in
Cancer and Chronic Inflammatory
Diseases: The Role of
Desensitizations.
Front. Immunol. 8:1472.
doi: 10.3389/fimmu.2017.01472

Drug allergy is a rising problem in the twenty-first century which affects all populations and races, children, and adults, and for which the recognition, diagnosis, management, and treatment is still not well standardized. Classical and new chemotherapy drugs, monoclonal antibodies (MoAbs), and small molecules to treat cancer and chronic inflammatory diseases are aimed at improving quality of life and life expectancy of patients, but an increasing number of reactions including anaphylaxis precludes their use in targeted populations. Women are more affected by drug allergy and up to 27% of women with ovarian and breast cancer develop carboplatin allergy after multiple cycles of treatment. Carriers of BRCA genes develop drug allergy after fewer exposures and can present with severe reactions, including anaphylaxis. Atopic patients are at increased risk for chemotherapy and MoAbs drug allergy and the current patterns of treatment with recurrent and intermittent drug exposures may favor the development of drug allergies. To overcome drug allergy, desensitization has been developed, a novel approach which provides a unique opportunity to protect against anaphylaxis and to improve clinical outcomes. There is evidence that inhibitory mechanisms blocking IgE/antigen mast cell activation are active during desensitization, enhancing safety. Whether desensitization modulates drug allergic and anaphylactic responses facilitating tolerance is currently being investigated. This review provides insight into the current knowledge of drug allergy and anaphylaxis to cancer and chronic inflammatory diseases drugs, the mechanisms of drug desensitization and its applications to personalized medicine.

Keywords: desensitization, monoclonal antibodies in cancer, platins, drug allergy, taxanes

INTRODUCTION

With the unprecedented use of chemotherapies drugs and targeted monoclonal antibodies (MoAbs) and small molecules in the twenty-first century, increased hypersensitivity reactions (HSRs) have emerged worldwide (1, 2). Drug allergic reactions are unexpected, can be severe including anaphylaxis and prevent the use of first-line therapies, with consequent impact in patient's survival and quality of life (3, 4). These reactions range from mild cutaneous manifestations such as pruritus and hives to life-threatening anaphylaxis with hypotension, oxygen desaturation and cardiovascular collapse, and deaths have been reported after re-exposure to allergic drugs (5, 6). The presentation of symptoms can be atypical such as pain, which has been associated with taxanes reactions, and chills and fever which have been seen with oxaliplatin and MoAbs reactions (7, 8). Delayed reactions occurring

more than 24 h after chemotherapy infusions can be due to the prolonged half-life of MoAbs and the presence of premedications, which may mask the acute phase of the reactions (9, 10).

The traditional classification of drug hypersensitivity and allergy into the classical types I–IV does not encompass the current spectrum of reactions and symptoms occurring in cancer patients and patients with chronic inflammatory diseases (11, 12). Some of the reactions have no known underlying mechanism, others have a known mechanism which is not part of the four described types and some drugs can induce mixed reactions with two or more proposed mechanisms (13, 14). Hypersensitivity to rituximab, a chimeric anti-CD20 MoAb, can induce cytokine-like reactions with chills, fevers, hypotension, and oxygen desaturation, which have been attributed to the release of cytokines such as IL-6, IL-1 β , and TNF- α and are named cytokine release syndrome or cytokine storm, which is not contemplated in the Gell and Coombs classification (15). In contrast, some patients have classical IgE-mediated reactions to rituximab and have presented positive skin testing demonstrating that IgE and mast cells are part of the underlying mechanism (16). Some patients reactive to oxaliplatin present mixed reactions with Type I features such as hives and hypotension, along with fever and chills as seen in cytokine storm-like reactions, presenting a complex mixed pattern of reactivity which provides challenges to management and treatment (17). During mixed reactions tryptase, the major mast cell protease, and IL-6 can be elevated in serum indicating mast cell activation and cytokine release from unknown cellular sources. Reactions to taxenes can trigger direct mast cell/basophil activation with elevation of serum tryptase with or without evidence of IgE, indicating that more than one mechanism can explain taxane hypersensitivity. A different receptor than Fc ϵ RI, such as the recently described MrgprX2 for drugs with THIQ motifs such as quinolones and paralyzing agents such as atracurium could be activated during non-IgE taxane reactions (13, 18–20).

Patients presenting with delayed cutaneous reactions are at a great concern for Stevens–Johnson syndrome and toxic epidermal necrolysis, two life-threatening conditions which can lead to permanent disability, blindness, and dramatic decrease in the quality of life for survivors (16, 21). The underlying mechanisms of the reactions are poorly understood and up to now no predictive markers have been available. Genetic susceptibility and defined HLA haplotypes are thought to be risk factors for some of the reactions, such as HLA-B 5701 in HIV patients reactive to abacavir. In patients with targeted haplotypes, a new role for viral reactivation of HHV6 and other virus have been demonstrated, and the pathogenic role of the virus is under study (22–24).

To provide an operational classification which can adapt to the increasing knowledge of the mechanisms of reactions and to the symptoms and clinical presentations, a recent initiative has provided a new terminology, applicable to precision medicine. In the new categorization drug allergy phenotypes are defined by the underlying endotypes and associated biomarkers and can be used in personalized medicine, with each patient being categorized according to her/his symptoms complex presentation. Current phenotypes include acute and delayed reactions with IgE and

non-IgE involvement, cytokine storm, and mixed patterns. The endotypes responsible for the expression of symptoms include mast cell and basophil activation through known receptors (Fc ϵ RI, Fc γ R, MRGPRX2) and directly through known receptors: complement, kinin and bradykinin activation and COX-1 inhibition. Associated biomarkers include serum tryptase, skin testing, basophil activation test, specific IgE and patch testing among others (13, 25–28).

Patients presenting with reactions compatible with phenotypes consistent with acute and delayed IgE and non-IgE, mast cell/basophil activation, and T cell activation endotypes may be prevented from the use of first-line therapies for fear of inducing anaphylaxis or more severe delayed reactions upon re-exposure to the allergenic drug. A groundbreaking procedure, desensitization, has emerged in the last 15 years as a proven effective and safe procedure to maintain patients on their first-line medications.

CLINICAL VIGNETTE

Mrs. MFF is a 49-year-old healthy female who was discovered to have ovarian cancer after a routine gynecology ultrasound and was initially treated with surgery and chemotherapy with six courses of carboplatin and paclitaxel and entered remission. Two years later, the CA125 is increased and new masses are found in her abdomen, a diagnosis of recurrent stage 4 ovarian cancer is made and carboplatin and paclitaxel restarted. After the second course of carboplatin, the patient feels her hands itchy but finished the infusion and did not have any further symptoms. On the day of her third infusion, the patient presented flushing, generalized pruritus, shortness of breath, and sudden dizziness. The blood pressure drops below normal range as well as the oxygen saturation and the patient has a syncopal episode and needs to be resuscitated with epinephrine, fluids, anti-histamines, and steroids. She recovers and her diagnosis is of anaphylaxis, a serum tryptase level during the episode is elevated at 52 ng/ml (normal range 11.4 ng/ml). The patient is evaluated for carboplatin allergy and skin testing is positive. Her options are to change to a second-line agent which is likely to reduce her life expectancy or to remain on first-line therapy with carboplatin but because of her anaphylactic reaction this option is not considered safe unless carboplatin can be introduced through desensitization, a powerful and novel intervention which has shown to protect patients against anaphylaxis and permit re-introduction of allergy drugs.

DRUG DESENSITIZATION

The term drug desensitization is currently used to define a process by which a patient's immune response to a drug is modified to generate temporary tolerance, taking advantage of well characterized inhibitory pathways (6). In the case of IgE-mediated drug allergy, positive skin testing and specific serum IgE can be used as biomarkers along with elevated serum tryptase level during the acute reaction (8, 11, 17). Patients without evidence of IgE mechanism are good candidates for desensitization provided the phenotype of the drug reaction is a type I or a type IV like reaction without features of SJS/TEN (16, 21, 29) (**Table 1**).

TABLE 1 | Indications, contraindications and risk factors for drug desensitization.

Indications	High-risk patients	Contraindications
Reactions 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 Use of beta-blockers, ACE inhibitors Pregnancy	Serum sickness-like (type III reactions)

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.

The mechanisms underlying drug desensitization are based on *in vitro* and *in vivo* models which have proposed that mast cells and basophils can be induced to predominantly inhibitory pathways by small incremental antigen doses, deactivating signal transduction and mediators release (13) (**Figure 1**).

Negative skin test is seen following desensitization in patients with IgE-mediated reactions, providing evidence of the powerful mechanisms which turn off skin mast cells (30–32). Partitioning of an optimal dose into 11–16 incremental doses starting at 1/1,000 the target dose and delivering them with sufficient time interval to mast cells; inhibits the acute release of beta-hexosaminidase, a mast cell granule mediator, prevents the generation of arachidonic acid and products such as leukotrienes and prostaglandins and the late generation of inflammatory cytokines (**Figure 1**) (13).

During desensitization, calcium influx is abolished and actin polymerization impaired, providing stability to intracellular granules in an antigen-specific fashion (**Figure 1**) (13). Membrane events that prevent internalization or modify its

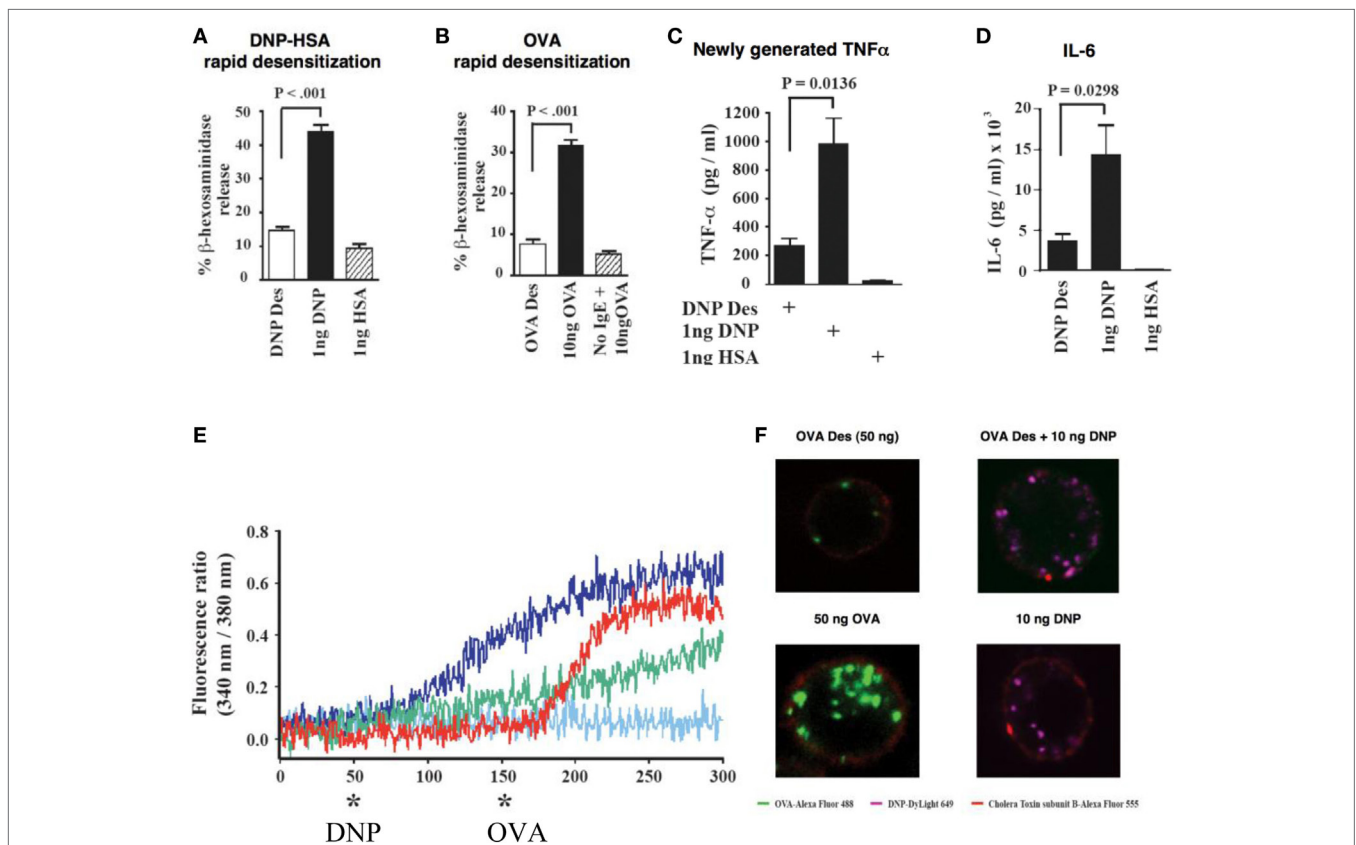
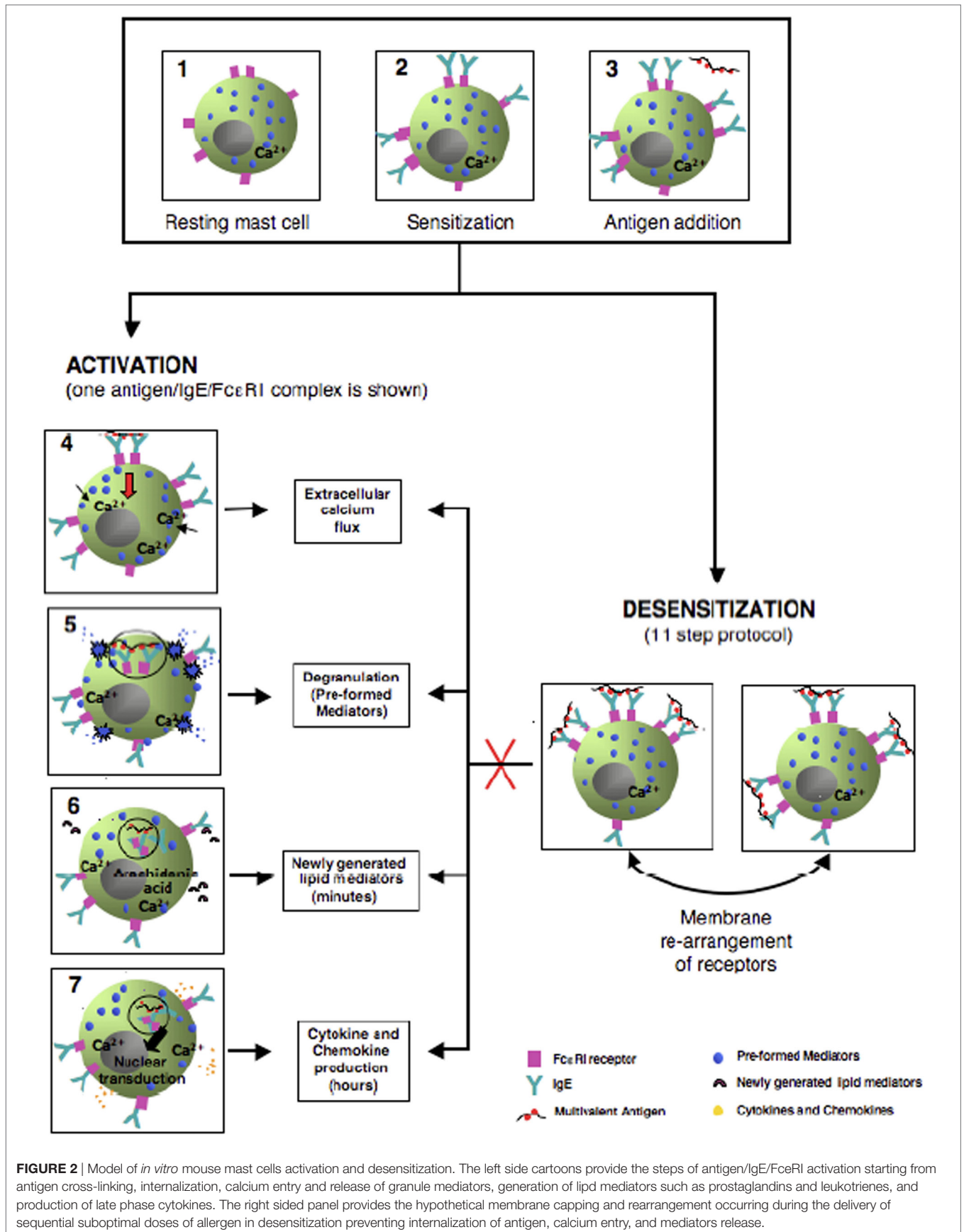
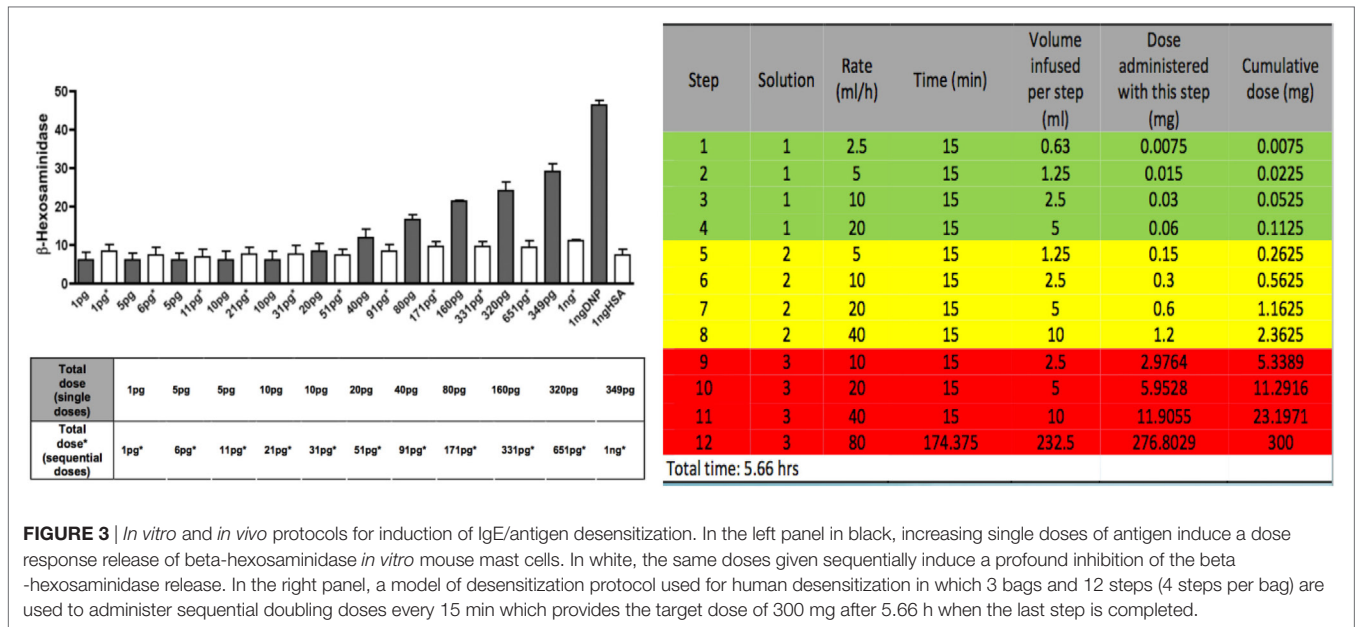


FIGURE 1 | *In vitro* IgE/antigen mouse mast cells activation and desensitization (13). **(A)** Desensitization of *in vitro* DNP-IgE sensitized mouse mast cells with DNP inhibits the release of granule mediators such as beta-hexosaminidase. Instead of one single optimal dose, 11 suboptimal sequential doses are given until reaching the optimal dose. **(B)** Desensitization of *in vitro* OVA-IgE sensitized mouse mast cells with OVA inhibits the release of granule mediators such as beta-hexosaminidase. Instead of one single optimal dose, 11 suboptimal sequential doses are given until reaching the optimal dose. **(C)** Desensitization of *in vitro* DNP-IgE sensitized mouse mast cell mediators with DNP inhibits the *de novo* generation of cytokines TNF alpha and IL-6. **(D)** Calcium entry (blue line) occurs after activation of DNP-IgE sensitized mouse mast cells with DNP but not when cells have been desensitized to DNP (red line, * DNP). Desensitization is specific since cells that were DNP desensitized and OVA-IgE sensitized presented calcium entry after OVA activation (red line, * OVA). **(E)** Membrane events are modified during desensitization with lack of internalization of desensitized antigens: left panels indicate that OVA desensitization does not present internalization of antigen (upper panel) as opposed to activation (lower panel with green labeled OVA internalized) and right panels indicate that after OVA desensitization another non desensitizing antigen such as DNP can be internalized (upper panel) as seen with activation (lower panel).



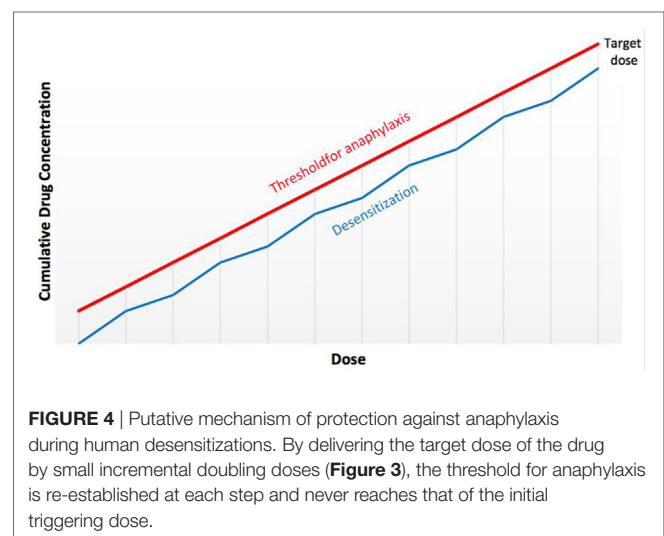


response to subthreshold doses of antigen occur during desensitization and are associated with incremental unresponsiveness to specific antigen (Figure 2) (13). Association of the FcεRI to ITIM containing receptors, capable of dephosphorylating ITAMs receptors has been postulated as one of the mechanisms of desensitization. Mast cells desensitized to one antigen are responsive to a second non desensitizing antigen, providing evidence of compartmentalization and highly specialized and regulated intracellular processes (Figure 1) (13).

The protocols used for *in vitro* desensitization have been adapted *in vivo* and further adaptations have produced safe protocols for human use (Figure 3) with similar dose increments and interval times (25–28). These human protocols have now been used in thousands of cases with remarkable safety since the inhibitory mechanisms of desensitization protect against anaphylaxis (Figure 4) (33, 34).

Whether after multiple desensitizations neutralizing antibodies can be generated which may block allergenic drug epitopes has been hypothesized (6). Maintaining drug desensitization state depends upon continued drug exposure and desensitized drugs require administration at regular intervals to maintain a stable pharmacokinetics state. Desensitization needs to be repeated if several half-lives of the medication have elapsed (6, 33).

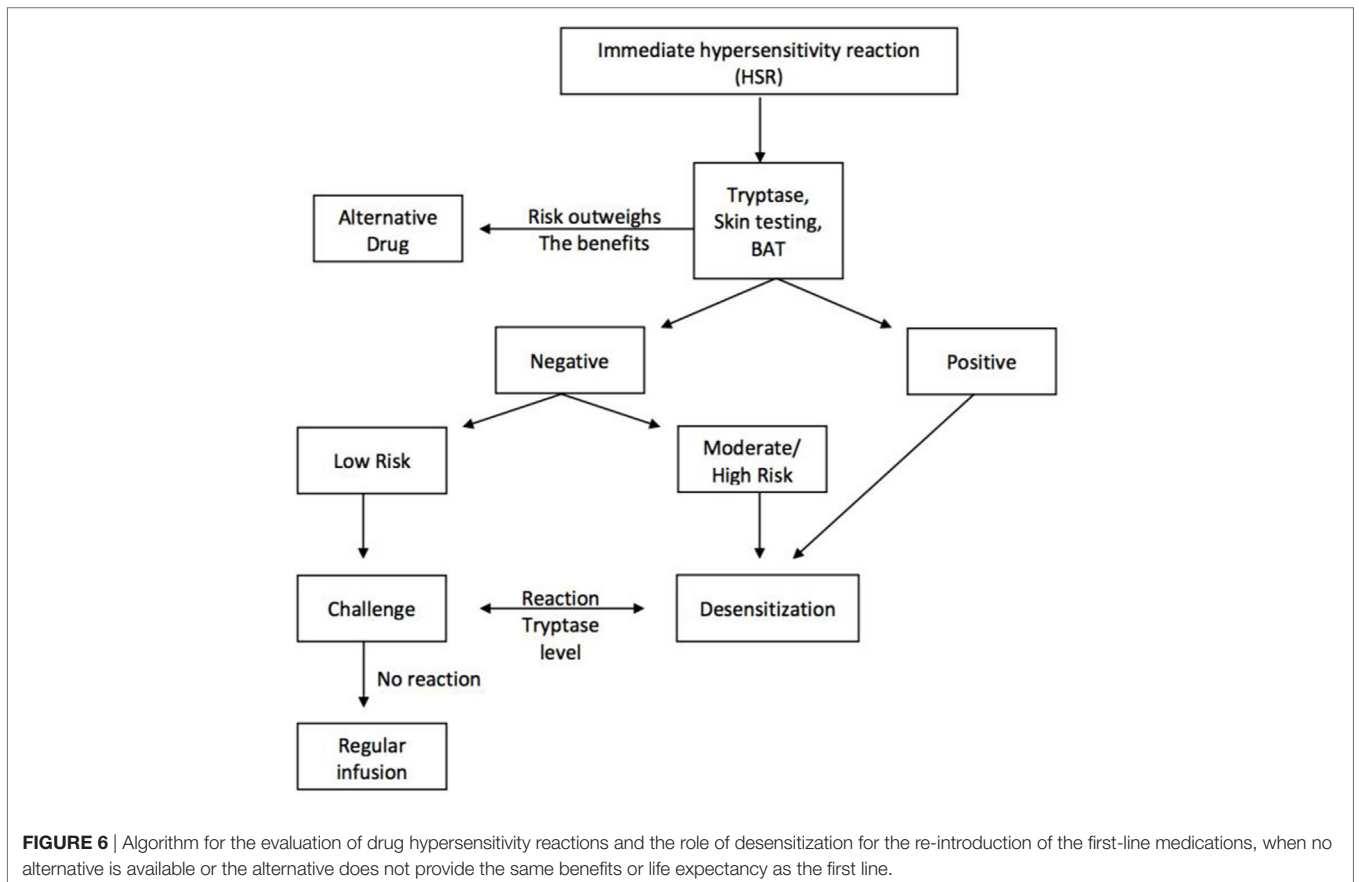
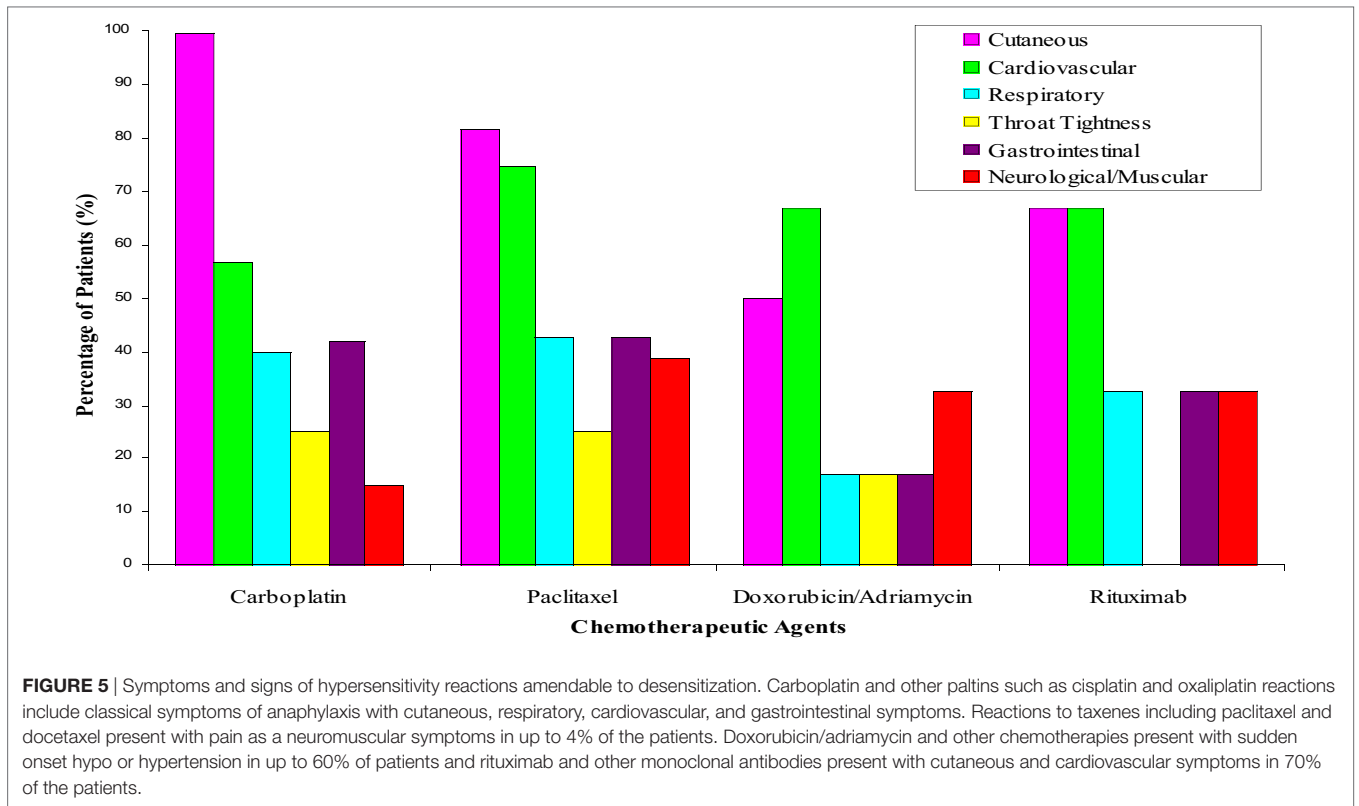
Protocols for drug desensitization have been successfully used for antibiotics, chemotherapy drugs, and MoAbs among other drugs in patients with IgE and non-IgE-mediated HSRs (Figure 5) (6, 14, 33, 35). The phenotypes of reactions amendable to desensitization include immediate and delayed reactions. Typical type I reactions usually begin within minutes of initiation of the infusion to few hours after the infusion due to anti-histamine and steroid premedication. The signs and symptoms include pruritus, flushing, urticaria, angioedema, throat tightening, wheezing, nausea, diarrhea, hypotension, syncope, seizures, and cardiovascular collapse which can lead to death. Atypical symptoms include back,



chest, or abdominal pain (such as seen with taxanes, oxaliplatin, MoAbs such as rituximab) (33, 35).

Delayed reactions are attributed to type IV reactions and can occur several days after the infusion and are typically limited to the skin with maculopapular rashes (36). Reactions that involve mucosal membranes and/or are associated with systemic symptoms are not amendable to desensitization due to the risk of inducing a severe systemic reaction with small amounts of drug antigen (16, 21, 29).

Desensitization should be considered in patients with reaction phenotypes consistent with type I and type IV reactions who have no alternative therapy or for whom alternative therapies are of less value or can induce more side effects. The algorithm for the evaluation of these patients is seen in Figure 6 (6, 34, 37). The



nature and symptoms of the initial reactions needs to be established and tryptase and skin test provide evidence of IgE and/or mast cell involvement. BAT is a research tool and cannot be applied to current clinical practice.

Drug desensitization can be performed in patients of any age and in pregnant women when alternative therapies are not possible or when delaying therapy may incur a shortened life span. Anaphylaxis is the major risk during desensitization since patients are exposed to their allergic drug. Large series have demonstrated that most breakthrough reactions during desensitization are mild and less severe than the patient's initial HSR and fatalities have not been reported, but all desensitizations can only be performed by an expert allergist familiar with the personalized protocol and potential reactions (Table 1) (17, 33, 35). The safety of desensitizations is paramount and patients with grade 3 severe initial reactions and anaphylaxis can be desensitized with minimal reactions as seen in Table 2.

Desensitization is not recommended for type II and type III serum sickness-like reactions or in patients with reactions with skin desquamation, EM, Stevens–Johnson syndrome or toxic epidermal necrolysis, because small amounts of drug can induce irreversible and potentially fatal reactions (Table 1) (16, 21, 29).

The most commonly used intravenous desensitization protocols are standardized 12- to 16-step protocols modeled after *in vitro* protocols and can be personalized to all drugs with adjustment of the target dose, time intervals between doses and starting dose (Figure 3) (33, 38). Protocols are available for intravenous desensitizations but also for oral, subcutaneous, intraperitoneal, or intravenous routes in the outpatient and inpatient settings (39–41). Desensitization for delayed reactions is also available and may take several days but recent data suggest that some of these reactions may be amenable to shorter time intervals (8, 36, 42). The overall safety of desensitizations is similar for all medications provided the mechanism of the initial reaction is of type I, IgE and non-IgE or type IV. As seen in Figure 7, the overall safety indicates that 93% of patients present with no reaction or grade 1 reactions and all completed the desensitization.

Platins, taxanes, and MoAbs are the most common chemotherapy currently used in desensitization and are described below.

Platin Hypersensitivity

Platinum compounds are used in ovarian, colorectal, endometrial, glioblastoma, lung, and pancreatic cancer as initial chemotherapy

and in second-line or salvage settings. Carboplatin is the most popular since it is less nephrotoxic and neurotoxic than cisplatin. Allergic reactions to platins are IgE-mediated and require sensitization through multiple exposures, with 27% of women becoming allergic after seven life time exposures (12, 43, 44). Allergic symptoms typically start at the second round of treatment, when the cancer recurs and after 1–2 exposures sensitized patients present with flushing and pruritus which can progress to shortness of breath with further exposure and can lead to anaphylaxis, with hypotension and cardiovascular collapse (2, 4, 7, 33, 45). Patients bearing BRCA 1 and 2 gene mutations have an increased risk for carboplatin reactions, which can occur with fewer exposures (46, 47). Most reactions to platins occur during or shortly after the drug infusion and the phenotype is that of type I reaction. In a study of 60 carboplatin sensitized patients, 100% had cutaneous, 60% pulmonary, 40% respiratory, and 42% gastrointestinal symptoms (6).

The phenotype of reactions to oxaliplatin can be more complex with features including typical IgE-mediated symptoms and atypical symptoms such as back and pelvic pain and cytokine-mediated fever and chills (7, 11, 17, 48, 49). Antibody-mediated thrombocytopenia and immune complex-mediated syndromes with urticaria and proteinuria have also been observed (17, 50).

Skin testing to platins has been safely done (Table 3) and is diagnostic tool to demonstrate an IgE/mast cell mechanism in patients with carboplatin and cisplatin reactions (7, 11, 17). For patients exposed to six or more courses of carboplatin in the last 6 months the positive predictive value is up to 86% (11). Oxaliplatin skin testing is negative in up to 50% of patients presenting type I reactions, indicating other than IgE mechanisms or lack of skin test allergenic determinants (17). Circulating serum specific IgE has been demonstrated and patients reactive to oxaliplatin with detectable serum-specific IgE have also demonstrated IgE to carboplatin and cisplatin without exposure, indicating broad cross-reactivity (51). IgE to platins can be short lived since a study has demonstrated that ST is negative in a high proportion of patients with a remote history of HSR to carboplatin, but re-exposure leads to resensitization and severe reactions (11). When platins are considered as first-line therapy, desensitization is a safe option since increased premedications alone do not prevent anaphylaxis and cross-reactivity may prevent the use of other platins (51). Patients with severe cutaneous reactions, SJS and TEN are currently not candidates since the mechanism of the reactions is unknown and small amounts of medications may induce severe symptoms (1, 16, 21, 29). Desensitization provides a similar life expectancy as non-allergic non desensitized patients (Figure 8) without increased health costs (33).

Taxanes

Taxanes are used in gynecologic, lung, breast, and prostate cancers and reactions to taxanes are among the most frequent chemotherapy reactions and fatalities have been reported (52). Paclitaxel and docetaxel have been the more frequently used and more recently other taxanes such as cabazitaxel and abraxane have become popular (53). Paclitaxel is an insoluble compound originally isolated from the bark of the pacific yew tree, *Taxus*

TABLE 2 | Safety of first desensitization in patients with grades 1, 2, and 3 initial reactions.

Initial hypersensitivity reaction grade	First desensitization reaction grade				Total
	0	1	2	3	
1	76 (61%)	38 (30%)	7 (6%)	4 (3%)	125
2	38 (58%)	22 (34%)	4 (6%)	1 (2%)	65
3	122 (60%)	54 (26%)	10 (5%)	19 (9%)	205
Total	236	114	21	24	396

From Sloane et al. (33).

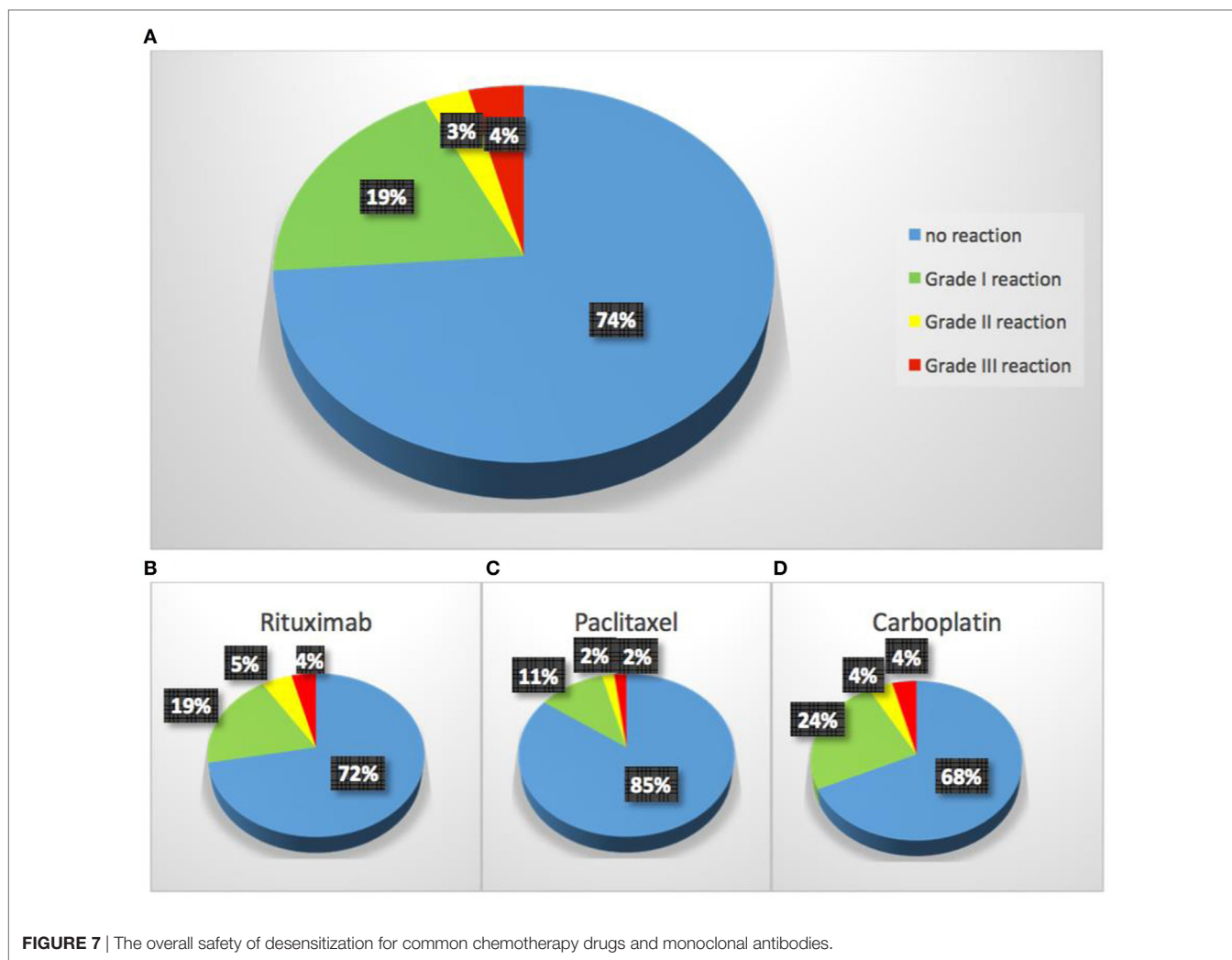


TABLE 3 | Skin testing for the diagnosis of chemotherapy drug allergy including platins, monoclonal antibodies, and paclitaxel.

Medication	Prick (mg/ml)	Intradermal (mg/ml)
Carboplatin	10	0.1, 1, 5, and 10
Cisplatin	1	0.1 and 1
Oxaliplatin	5	0.5 and 5
Rituximab	10	0.1, 1, and 10
Infliximab	10	0.1, 1, and 10
Tocilizumab	20	0.2, 2, and 20
Centuximab	20	0.2, 2, and 20
Trastuzumab	21	0.21, 2.1, and 21
Bevacizumab	25	0.25, 2.5, and 25
Cyclophosphamide	10	0.1, 1, and 10
Methotrexate	25	0.2, 2.5, and 25
Paclitaxel	1–6	0.001 and 0.01

Baccata tree and solubilized in cremophor and docetaxel is a semi-synthetic molecule derived from a precursor found in European yew tree needles and solubilized in polysorbate 80 (36, 54). The solvents can cause complement activation, generating anaphylotoxins C3a and C5a and leading to mast cell

activation (55–57). Taxanes are used with premedications including anti-histamines and steroids due to a high rate of reactions in early clinical studies (54). The rate of reaction has decreased to less than 10% and typically occurs during the first or second lifetime exposure in up to 80% of the patients (54). The phenotype of the reactions include type I symptoms such as throat tightness, flushing, hypotension, and dyspnea but atypical symptoms such as chest, back, or pelvic pain (8, 36, 54).

Skin testing has uncovered IgE-mediated reactions to taxanes and a recent study reported that 103 of 145 taxane reactive patients (71%) had positive results. Negative skin test patients who were challenged were likely to tolerate taxane infusions without desensitization. Atopy was present in over 40% of the patients and because patients react at first or second exposure suggested prior sensitization or cross-reactivity with environmental allergens (8). Risk stratification based on biomarkers such as skin testing can safely guide the management to taxane reactions and allows a significant number of patients to resume regular infusions. For patients with positive skin test and significant initial reaction for whom taxanes are first-line therapy, desensitization should be considered (8).

Monoclonal Antibodies

There are over 45 MoAbs currently in use for the treatment of cancer and inflammatory and autoimmune diseases. Reactions to MoAbs depend on their structure and vary from chimeric mouse-human, humanized, to fully human. Some of the most frequently used MoAbs are presented in **Table 4**, including their targets, incidence of overall injection/infusion site reactions, and HSRs (19, 34, 35).

Monoclonal antibodies immunogenicity depends on the human content but fully human MoAbs, such as adalimumab

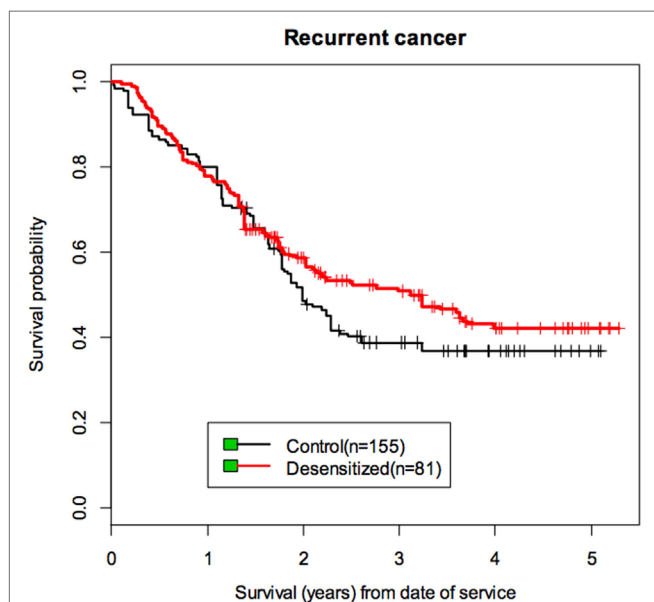


FIGURE 8 | Life expectancy for cancer patients allergic and desensitized to carboplatin and non-allergic to carboplatin [from Sloane et al. (33)]. Allergic and non-allergic ovarian cancer patients treated with carboplatin or carboplatin desensitization presented a similar life expectancy with a non significant advantage for the allergy desensitized patients.

and ofatumumab can induce severe HSRs likely due to the glycosylation patterns *in vitro* and the generation of neo antigens (58). This is best exemplified in reactions to cituximab which can occur at first exposure in patients sensitized through tick bites to the mammalian oligosaccharide epitope, galactose- α -1,3-galactose (α -gal) (59).

The phenotypes of MoAbs reactions include limited infusion reactions, IgE-mediated reactions, serum sickness-like reactions, cytokine storm-like reactions, and mixed reactions. Infusion reactions are characterized by nausea, chills, fever, and malaise and for trastuzumab these reactions can occur in up to 40% of patients (34, 35). Like cytokine storm-like reactions, which are more severe, can associate with hypotension, oxygen desaturation, and require treatment with steroids and COX-1 inhibitors, proinflammatory cytokines (such as IL-6 and TNF- α) are thought to be involved (60, 61).

Immediate and delayed HSRs can occur with MoAbs and serum sickness-like reactions, such as seen with infliximab and omalizumab, which can present with rash, myalgia, fever, polyarthralgias, pruritus, edema, and fatigue (35).

Monoclonal antibodies used subcutaneously can elicit injection-site reactions few hours after the injection and persisting for several days. The phenotype of these reactions include local redness, warmth, burning, itching, urticaria, pain, and induration, varying in frequency from 0.8 to 4.5% with certolizumab to up to 45% with omalizumab (39).

Reactions to MoAbs can occur during the infusion and should prompt interruption of the treatment and the evaluation of tryptase and inflammatory cytokines to further understand the mechanism of the reactions. Skin testing with the offending agent can be done for type I and mixed reactions 2–4 weeks after the reaction to avoid false negative results, in particular in anaphylactic reactions in which natural desensitization can occur (35). An important consideration is cost of MoAbs; there are no available reagents at the present time for the evaluation of MoAb reactions and using a treatment vial may exceed several thousand dollars, precluding a diagnostic skin test evaluation. The negative

TABLE 4 | Common monoclonal antibodies in use and rate of overall reactions and hypersensitivity reactions (HSR).

Drug	Target	Overall reactions	HSR
Rituximab (Rituxan®) IV	CD20	77% (first infusion) (52)	5–10% (53)
Ofatumumab (Arzerra®) IV	CD20	44% (first infusion) (54) 67% (combination therapy) (55)	2% (55)
Obinutuzumab (Gazyva®) IV	CD20	66% (56,57)	(58)*
Trastuzumab (Herceptin®) IV	HER-2	40% (mild; first infusion) (59)	0.6–5% (60)
Cetuximab (Erbix®) IV	EGFR	15–21% (61)	1.1–5% (62–65) 14–27% (Southern USA) (43,66,67)
Tocilizumab (Actemra®) IV	IL-6 receptor	7–8% (68)	0.1–0.7% (68)
Infliximab (Remicade®) IV	TNF- α	5–18% (69)	1%* (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% (76)	(77–79)*
Bevacizumab (Avastin®) IV	VEGF-A	<3% (80)	Not reported
Omalizumab (Xolair®) SC	IgE	45% (81)	00.9–0.2% (81,82)

* $p < 0.05$

predictive value of skin testing is not known and in a study of 23 patients reactive to trastuzumab, infliximab, or rituximab, 13 patients had positive skin test. Positive and negative skin test patient with significant initial reactions are candidates for desensitization and subcutaneous protocols are available. Successful desensitizations to rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab have been reported (33–35).

CONCLUSION

Drug hypersensitivity is an increasing health hazard, which can compromise the quality of life and the life expectancy of cancer patients and patients with chronic inflammatory diseases with reactions to their first-line therapy. Recognition of the mechanisms of the reactions into phenotypes, understanding the underlying endotypes and evaluation of biomarkers is key to personalized medicine and enhanced patient safety allowing for informed decisions regarding drug re-exposure and desensitization.

REFERENCES

- Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: data mining of the public version of the FDA adverse event reporting system, AERS. *J Exp Clin Cancer Res* (2011) 30:93. doi:10.1186/1756-9966-30-93
- Sakaeda T, Kadoyama K, Yabuuchi H, Nijima S, Seki K, Shiraishi Y, et al. Platinum agent-induced hypersensitivity reactions: data mining of the public version of the FDA adverse event reporting system, AERS. *Int J Med Sci* (2011) 8(4):332–8. doi:10.7150/ijms.8.332
- Nektaria M, Ekaterini S, Ioannis K, Leonidas M, Muhammad Wasif S. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* (2010) 2010. Available from: <http://downloads.hindawi.com/journals/mbd/2010/207084.pdf>
- Markman M. Toxicities of the platinum antineoplastic agents. *Expert Opin Drug Saf* (2003) 2(6):597–607. doi:10.1517/14740338.2.6.597
- A fatal anaphylactic reaction to paclitaxel is described, which was preceded by a possible delayed reaction to the initial infusion. *Allergy Asthma Proc* (2011) 32(1):79. doi:10.2500/aap.2011.32.3409
- Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* (2008) 122(3):574–80. doi:10.1016/j.jaci.2008.02.044
- Caiado J, Castells M. Presentation and diagnosis of hypersensitivity to platinum drugs. *Curr Allergy Asthma Rep* (2015) 15(4):15. doi:10.1007/s11882-015-0515-3
- Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* (2016) 137(4):1154–64.e1–12. doi:10.1016/j.jaci.2015.10.039
- Feldweg AM, Lee C-W, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* (2005) 96(3):824–9. doi:10.1016/j.ygyno.2004.11.043
- Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity, and associated infusion reactions. *Mt Sinai J Med* (2005) 72(4):250–6.
- Wang AL, Patil SU, Long AA, Banerji A. Risk-stratification protocol for carboplatin and oxaliplatin hypersensitivity: repeat skin testing to identify drug allergy. *Ann Allergy Asthma Immunol* (2015) 115(5):422–8. doi:10.1016/j.anai.2015.07.017
- Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol* (2012) 129(2):443–7. doi:10.1016/j.jaci.2011.10.010
- Sancho-Serra Mdel C, Simarro M, Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization. *Eur J Immunol* (2011) 41(4):1004–13. doi:10.1002/eji.201040810
- Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Sancho-Serra M, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy* (2011) 41(12):1679–89. doi:10.1111/j.1365-2222.2011.03825.x
- Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness-like reactions in patients receiving intravenous infliximab. *J Emerg Med* (2006) 30(1):41–4. doi:10.1016/j.jemermed.2005.01.033
- Phillips EJ, Chung W-H, Mockenhaupt M, Roujeau J-C, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol* (2011) 127(3 Suppl):S60–6. doi:10.1016/j.jaci.2010.11.046
- Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin hypersensitivity: evaluation, implications of skin testing, and desensitization. *J Allergy Clin Immunol Pract* (2014) 2(1):40–5. doi:10.1016/j.jaip.2013.08.011
- McNeil BD, Pundir P, Meeker S, Han L, Udem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* (2015) 519(7542):237–41. doi:10.1038/nature14022
- Muraro A, Lemanske RF, Castells M, Torres MJ, Khan D, Simon HU, et al. Precision medicine in allergic disease – food allergy, drug allergy, and anaphylaxis-PRAC-TALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *Allergy* (2017). Available from: <http://onlinelibrary.wiley.com/doi/10.1111/all.13132/full>
- Garon SL, Pavlos RK, White KD, Brown NJ, Stone CA, Phillips EJ. Pharmacogenomics of off-target ADRs. *Br J Clin Pharmacol* (2017). Available from: <http://onlinelibrary.wiley.com/doi/10.1111/bcp.13294/full>
- Bachot N, Roujeau J-C. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* (2003) 4(8):561–72. doi:10.2165/00128071-200304080-00006
- Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B* 5701 screening for hypersensitivity to abacavir. *N Engl J Med* (2008) 358(6):568–79. doi:10.1056/NEJMoa0706135
- Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B* 5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* (2002) 359(9308):727–32. doi:10.1016/S0140-6736(02)07873-X
- Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* (2002) 359(9312):1121–2. doi:10.1016/S0140-6736(02)08158-8

25. Ang WXG. *Methods and Mechanisms of Mitigating Mast Cell Activation in Anaphylaxis*. (2016). Available from: <https://pdfs.semanticscholar.org/77e7/3874cddabe5b9423e1b25b2b4abaf4190b40.pdf>
26. Ang WXG, Church AM, Kulis M, Choi HW, Burks AW, Abraham SN. Mast cell desensitization inhibits calcium flux and aberrantly remodels actin. *J Clin Invest* (2016) 126(11):4103–18. doi:10.1172/JCI87492
27. Oka T, Rios EJ, Tsai M, Kalesnikoff J, Galli SJ. Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. *J Allergy Clin Immunol* (2013) 132(4):922–32.e1–16. doi:10.1016/j.jaci.2013.05.004
28. Morales AR, Shah N, Castells M. Antigen-IgE desensitization in signal transducer and activator of transcription 6-deficient mast cells by suboptimal doses of antigen. *Ann Allergy Asthma Immunol* (2005) 94(5):575–80. doi:10.1016/S1081-1206(10)61136-2
29. Pirmohamed M, Friedmann PS, Molokhia M, Loke YK, Smith C, Phillips E, et al. Phenotype standardization for immune-mediated drug-induced skin injury. *Clin Pharmacol Ther* (2011) 89(6):896–901. doi:10.1038/clpt.2011.79
30. Cernadas JR, Brockow K, Romano A, Aberer W, Torres MJ, Bircher A, et al. General considerations on rapid desensitization for drug hypersensitivity – a consensus statement. *Allergy* (2010) 65(11):1357–66. doi:10.1111/j.1398-9995.2010.02441.x
31. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* (2002) 57(1):45–51. doi:10.1034/j.1398-9995.2002.13027.x
32. MacGlashan DW Jr. IgE-dependent signaling as a therapeutic target for allergies. *Trends Pharmacol Sci* (2012) 33(9):502–9. doi:10.1016/j.tips.2012.06.002
33. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract* (2016) 4(3):497–504. doi:10.1016/j.jaip.2015.12.019
34. Bonamichi-Santos R, Castells M. Diagnoses and management of drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: reactions to taxanes and monoclonal antibodies. *Clin Rev Allergy Immunol* (2016) 1–11. doi:10.1007/s12016-016-8556-5
35. Brennan PJ, Rodriguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* (2009) 124(6):1259–66. doi:10.1016/j.jaci.2009.09.009
36. Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. *Clin Rev Allergy Immunol* (2015) 49(2):177–91. doi:10.1007/s12016-014-8416-0
37. Giavina-Bianchi P, Galvão VR, Picard M, Caiado J, Castells MC. Basophil activation test is a relevant biomarker of the outcome of rapid desensitization in platinum compounds-allergy. *J Allergy Clin Immunol Pract* (2017) 5:728–36. doi:10.1016/j.jaip.2016.11.006
38. Lee C-W, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol* (2004) 95(2):370–6. doi:10.1016/j.ygyno.2004.08.002
39. Bavbek S, Ataman Ş, Akıncı A, Castells M. Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients. *J Allergy Clin Immunol Pract* (2015) 3(4):629–32. doi:10.1016/j.jaip.2015.01.009
40. Nucera E, Schiavino D, Hohaus S, Leone G, Buonomo A, Lombardo C, et al. Desensitization to thalidomide in a patient with multiple myeloma. *Clin Lymphoma Myeloma* (2008) 8(3):176–8. doi:10.3816/CLM.2008.n.022
41. Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* (2009) 102(2):155–60. doi:10.1016/S1081-1206(10)60247-5
42. Clayton E, Madamba J, Kong X-T, Brskett M. Successful desensitization protocol for delayed cutaneous eruption to temozolomide. *J Allergy Clin Immunol Pract* (2014) 2(5):626–8. doi:10.1016/j.jaip.2014.03.016
43. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* (2009) 123(6):1262–7.e1. doi:10.1016/j.jaci.2009.02.042
44. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* (1999) 17(4):1141. doi:10.1200/JCO.1999.17.4.1141
45. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al. Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. *Oncology* (2001) 61(2):129–33. doi:10.1159/000055363
46. Moon DH, Lee JM, Noonan AM, Annunziata CM, Minasian L, Houston N, et al. Deleterious BRCA1/2 mutation is an independent risk factor for carboplatin hypersensitivity reactions. *Br J Cancer* (2013) 109(4):1072–8. doi:10.1038/bjc.2013.389
47. Galvão VR, Phillips E, Giavina-Bianchi P, Castells MC. Carboplatin-allergic patients undergoing desensitization: prevalence and impact of the BRCA 1/2 mutation. *J Allergy Clin Immunol Pract* (2017) 5(3):816–8. doi:10.1016/j.jaip.2016.08.012
48. Thomas RR, Quinn MG, Schuler B, Grem JL. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* (2003) 97(9):2301–7. doi:10.1002/cncr.11379
49. Maindrault-Goebel E, André T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N, et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J Cancer* (2005) 41(15):2262–7. doi:10.1016/j.ejca.2005.06.021
50. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: focus on hypersensitivity responses. *Oncoimmunology* (2013) 2(10):e26333. doi:10.4161/onci.26333
51. Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M. Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract* (2013) 1(5):494–500. doi:10.1016/j.jaip.2013.06.002
52. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol* (2009) 102(3):179–87; quiz 187–9, 222. doi:10.1016/S1081-1206(10)60078-6
53. Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R, et al. Phase III randomized trial of docetaxel–carboplatin versus paclitaxel–carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* (2004) 96(22):1682–91. doi:10.1093/jnci/djh323
54. Squibb B-M. *TAXOL® (Paclitaxel) Injection Prescribing Information*. FDA, (2012).
55. Qiu S, Liu Z, Hou L, Li Y, Wang J, Wang H, et al. Complement activation associated with polysorbate 80 in beagle dogs. *Int Immunopharmacol* (2013) 15(1):144–9. doi:10.1016/j.intimp.2012.10.021
56. Weiszhar Z, Czucz J, Révész C, Rosivall L, Szebeni J, Rozsnyay Z. Complement activation by polyethoxylated pharmaceutical surfactants: cremophor-EL, tween-80 and tween-20. *Eur J Pharm Sci* (2012) 45(4):492–8. doi:10.1016/j.ejps.2011.09.016
57. Hennenfent KL, Govindan R. Novel formulations of taxanes: a review. Old wine in a new bottle? *Ann Oncol* (2006) 17(5):735–49. doi:10.1093/annonc/mdj100
58. Sheeley DM, Merrill BM, Taylor LC. Characterization of monoclonal antibody glycosylation: comparison of expression systems and identification of terminal alpha-linked galactose. *Anal Biochem* (1997) 247(1):102–10. doi:10.1006/abio.1997.2036
59. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* (2008) 358(11):1109–17. doi:10.1056/NEJMoa074943
60. Doessegger L, Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunology* (2015) 4(7):e39. doi:10.1038/cti.2015.14
61. Luheshi GN. Cytokines and fever. Mechanisms and sites of action. *Ann N Y Acad Sci* (1998) 856:83–9. doi:10.1111/j.1749-6632.1998.tb08316.x

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Castells. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.