Rapid Desensitization for Hypersensitivity Reactions to Medications

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KEYWORDS

• Desensitization • Antibiotics • Aspirin • Chemotherapy
• Monoclonal antibodies • Hypersensitivity reactions

The development of rapid desensitizations for the treatment of drug hypersensitivities is aimed at providing essential medications while protecting patients from IgE and non-IgE hypersensitivity reactions. Serious adverse drug reactions occur in 6.7% of hospitalized patients, and adverse drug reactions are the fourth to sixth leading cause of death in such patients.[1] Drug-induced type I hypersensitivity reactions, such as anaphylaxis, result from the release of mediators from IgE-sensitized mast cells and basophils. Drug-associated anaphylaxis can be triggered by β-lactam antibiotics, such as penicillin and cephalosporins, chemotherapy drugs, such as platins, therapeutic monoclonal antibodies, and others.[2–7] Cross-linking of IgE by drug antigens can lead to limited skin reactions (flushing, pruritus, urticaria, angioedema) or multiorgan system involvement (sneezing, sinus and nasal congestion, cough, shortness of breath, wheezing, abdominal pain, nausea, vomiting, diarrhea) with hypotension and cardiovascular collapse during anaphylaxis. Hypersensitivity reactions induced by drug antigens upon initial exposure, without prior sensitization and with symptoms similar to IgE-mediated reactions, are called ''non-IgE hypersensitivity reactions,'' and can result from direct release of mediators from mast cells and basophils, such in vancomycin-induced red man syndrome, intravenous contrast dyes, or taxenes. In these reactions, nontypical symptoms can occur, such as the severe back and muscle pain seen in patients with taxene and monoclonals reactions.[8]

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PRINCIPLES AND CELLULAR AND MOLECULAR TARGETS OF DRUG DESENSITIZATION

Desensitization for type I hypersensitivity reactions in penicillin-allergic patients were first developed 50 years ago.[9] Successful cases of rapid-progressive penicillin re-administration led to the concept of temporary clinical tolerization.[10,11] The administration of suboptimal doses of drug antigens, followed by the full therapeutic dose was safely achieved in highly allergic patients, permitting the treatment of severe infections. Following the early success with antibiotics, other empiric protocols were developed to treat hypersensitivity reactions to essential drugs that could not be substituted in allergic patients, such as aspirin in the control and prevention of cardiac diseases,[5] insulin in diabetes,[6] chemotherapy drugs during cancer recurrence,[12,13] and, more recently, chimeric and humanized monoclonal antibodies in chronic inflammatory diseases.[14] Because rapid desensitizations reintroduce potentially lethal drugs into highly sensitized patients, the molecular mechanisms need to be elucidated to improve the efficacy and safety of these procedures. Recent studies of in vitro rapid antigen desensitizations implicate mast cells and basophils as cellular targets, as well as syk,[15] a signal transducing molecule, and signal transducer and activator of transcription 6 (STAT6),[16] which is responsible for the transcription of interleukin (IL)-4 and IL-13.

CLINICAL MANIFESTATIONS

Hypersensitivity Reactions Type I, Mast Cell/IgE Dependent

Drug-induced hypersensitivity reactions type I result from the release of mediators from IgE-sensitized mast cells or basophils and can affect all organ systems, leading to anaphylaxis and death. Drug antigens can sensitize patients after multiple courses, and repeated exposures are needed for the development of specific IgE.[17] Sensitizing drugs can act as complete antigens, such as insulin, or haptens, which are coupled to a carrier protein, such as penicillin.[18] Among chemotherapy drugs, platins, such as carboplatin, cisplatin, and oxaliplatin can induce IgE formation[19] by a mechanism similar to that of metal workers exposed to low molecular-weight platinum salts by inhalation and skin contact.[20] Symptoms are induced by a platinum salt's cross-linking of specific IgE bound to high-affinity IgE receptors, FcεRI (on mast cells or basophils), with the release of membrane and granule mediators. These mediators include vasoactive amines, such as histamine, proteases such as tryptase, and proinflammatory and vasoactive prostaglandins and leukotrienes.[21]

Cross-linking of IgE by drug antigens can lead to limited skin reactions (flushing, pruritus, urticaria, angioedema) or multiorgan system involvement (sneezing, sinus and nasal congestion, cough, shortness of breath, wheezing, abdominal pain, nausea, vomiting, diarrhea), with decreased blood pressure and cardiovascular collapse during anaphylaxis. Reactions can occur within minutes of exposure and minimal amounts of the drug can induce severe reactions in highly sensitized individuals, such as laryngeal edema with asphyxiation. Disseminated intravascular coagulation and seizure-like acitivity are rare complications of anaphylaxis.[22] Retrospectively, finding an elevated tryptase in serum[23] and histamine in urine[24] can confirm the diagnosis.

The diagnosis of type I hypersensitivity reactions to drugs relies on the demonstration of in vivo or in vitro drug-specific IgE. Skin testing to drug antigens, such as penicillin, has a very high negative-predictive value. Only 1.8% to 3% of patients with a negative skin test present mild skin-limited reactions upon drug re-exposure.[25] Using different reagents, recent European data indicate a lower predictive value (see article by authors elsewhere in this issue). In a population of 126 patients who

received over six courses of carboplatin for recurrent ovarian cancer and were skin tested before each course, only 10 patients with negative skin test presented a hypersensitivity reaction, indicating that the rate of false-negative skin test is as low as 1.5%.[13] In the same population, 7 out of 41 patients with positive skin test were given carboplatin and all presented anaphylaxis. Eighty percent to 90% of patients reactive to present carboplatin have a positive skin test, indicating that the likelihood of a severe hypersensitivity reaction is very high in skin test-positive patients, and that rechallenging those patients is not indicated.

Hypersensitibity Reactions—Non-IgE Mediated

Hypersensitivity reactions induced by drug antigens upon initial exposure, without prior sensitization and with a similar clinical presentation and symptoms as IgE-mediated reactions are mostly considered non-IgE hypersensitivity reactions. Rarely, sensitization to a cross-reactive compound may occur (see article by authors elsewhere in this issue). They can result from the release of mediators from mast cells or basophils, without known IgE mechanism, and with a negative skin test.[26,27] Vancomycin-induced red man syndrome is caused by the direct release of histamine from mast cells and basophils.[28] Among chemotherapy drugs, taxenes can induce severe hypersensitivity symptoms, with cardiovascular collapse within few minutes of first exposure in patients who present a negative skin test. Mechanisms implicated in those reactions include the activation of complement by the diluent Cremophor[29] or the direct release of mediators. Reactions to aspirin and nonsteroidal anti-inflammatory medications include the inhibition of cyclooxygenase-1, decrease in bronchodilator prostaglandins E, and increased generation of inflammatory leukotrienes, as well as the release of tryptase from mast cell upon aspirin exposure in sensitive patients.[30–32]

CELLULAR AND MOLECULAR TARGETS

Although all clinical desensitization protocols are empiric and based on error and trial clinical experiences, in vitro desensitization of mast cells and basophils has provided some understanding of the mechanisms underlying successful in vivo desensitizations. Suboptimal doses of antigen, as low as one-tenth the optimal dose administered before an optimal dose, render mast cells and basophils unresponsive to antigens but not to other activating stimuli.[33] Suboptimal doses can induce unresponsiveness through excessive monomeric antigens, incapable of cross-linking surface FceRI receptors or through the rapid internalization of antigen cross-linked receptors depleting the cell surface.[34] Basophils can be desensitized in vitro to penicillin, but basophils isolated from a patient desensitized to penicillin were activated in vitro by penicillin antigens,[35] indicating that the presence of antigens at all times is critical to maintaining the desensitization state. In vitro rapid desensitization of human mast cells induces the decreased levels of signal-transducing molecules, such as syk, because of ubiquitinilation and degradation.[36,37] Naturally occurring syk-deficient basophils are unresponsive to drug antigens, indicating that syk is critical for activation and for desensitization.[15] In recent studies STAT6, which is responsible for the transcription of IL-4 and IL-13, has been involved in rapid desensitizations. STAT-6-deficient mast cells are capable of releasing mediators during the early phase of IgE cell activation but cannot release late cytokines, such as tumor necrosis factor (TNF)-α and IL-6, and cannot be desensitized to antigens.[16,38]

DESENSITIZATION TO ANTIBIOTICS

All antibiotics can induce IgE and non-IgE hypersensitivity reactions amendable to rapid desensitization, and the most common are β-lactams, including cephalosporins, vancomycin, and quinolones.

Penicillin and Cephalosporins

Patients allergic to penicillin are at risk when exposed to cephalosporins. Cross-reactivity between cephalosporins and penicillins is found in 4% to 11% of patients because of the related core β-lactam ring structure, mostly with first and second generation.[39] Specific cephalosporin IgE antibodies can be directed toward side-chain determinants that are not shared with β-lactam rings containing drugs,[40] posing less of a risk for penicillin-allergic patients. Other antibiotics containing β-lactam rings, such as monobactams (aztreonam), have no significant cross-reactivity with penicillins, and recently imipenem was shown to be tolerated by penicillin- and β-lactam-allergic patients.[41] Only immediate type I reactions to penicillin and β-lactams are amendable to rapid desensitization. Other reactions, such as maculopapular rashes, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous erythema, erythroderma, serum sickness, hemolytic anemia, neutropenia, thrombocytopenia, and acute interstitial nephropathy are not amendable to rapid desensitizations because outcomes are not available after drug re-exposure in these patients.

All patients with a history of IgE-mediated hypersensitivity and a positive skin test to either the minor or major penicillin determinants should avoid all β-lactam ring-containing medications, including penicillin, amoxicillin, ampicillin, and cephalosporins. Aztreonam and imipenem can be used as indicated by the infectious agents. If penicillin or cephalosporin treatment is mandated by the severity and nature of the infection, rapid desensitization is indicated.

Rapid Desensitization to β-Lactam antibiotics Including Penicillin and Cephalosporins

The first series of rapid penicillin desensitizations included escalating oral doses to treat 15 pregnant syphilis-infected women.[10] An intravenous protocol was later developed to treat 15 severely infected patients, which included 10-fold incremental doses[11] and induced 30% of nonlife-threatening side effects, including serum sickness. Since then, multiple case reports have been published with no series available to validate the efficacy and safety of the different protocols.

Up to 30% of cystic fibrosis patients develop hypersensitivity reactions after multiple exposures to β-lactams, which require rapid desensitizations.[42,43] A recent study indicated that 57 antibiotic desensitizations were done safely in 21 patients, 90% with cystic fibrosis. Most of the antibiotics were β-lactams and the success rate was 75%. Desensitization failures related to non-IgE mediated symptoms.[43]

A typical protocol for desensitization to intravenous penicillin and cephalosporins starts at one-ten-thousands to one-one-hundredth the target dose, and doubling doses are delivered every 15 to 20 minutes over the course of several hours until reaching the target dose.[44] Ceftazidime desensitization was done in seven cystic fibrosis patients to treat IgE-mediated hypersensitivity reactions,[45] with no major systemic reactions during desensitization. A recurrent rash occurred in two patients on the seventh and twelfth day after desensitization, one patient was successfully redesensitized, and one patient discontinued treatment. Cefotaxime desensitization was done in a 51-year-old man with bacterial spondylitis, and the treatment was continued for 4 weeks with no adverse events.[46] A series of eight patients with a positive skin test to penicillin and

cephalosporins (cefepime, ceftriaxone, and cefazolin) were desensitized to β-lactam drugs using a 2-hour and 15-minute protocol in which tripling doses were administered every 15 minutes, without major side effects.[47] An imipenem- and penicillin-allergic patient was desensitized to intravenous imipenem for multiresistant *Acinobacter pneumoniae* and the treatment was continued for 21 days without adverse events.[48]

The author and colleagues have used a standardized protocol at the Brigham and Women's Hospital in Boston, which includes a three solution, 12-step infusion allowing the patients to receive full therapeutic doses after 5.8 h (**Tables 1** and **2**). The solutions were made by 10-fold dilutions of the full target concentration (solution 3). Each solution was administered in four different steps. The rate of each step was increased every 15 minutes to deliver approximately twice the dose of the previous step. This model is based on the chemotherapy standard-desensitization protocol.[49] The author and colleagues performed 42 antibiotic successful desensitizations in 2005 and 2006 with this protocol (**Table 3**).[50] Side effects during antibiotic desensitizations were mild and included flushing, warmth, tingling, pruritus, erythema, rash, and hives. No serious events occurred, all subjects were treated for their full courses, and no late reactions were observed. Subjects were maintained on their antibiotics during the course of their treatments without need for repeated desensitizations.

Other Antibiotics

Vancomycin is an antimicrobial agent that is often used as an alternative treatment for serious staphylococcal and streptococcal infections in patients with hypersensitivity reactions to β-lactam antibiotics or whose infection failed to respond to β-lactam antibiotics. The incidence of adverse reactions has been reported to be in the range of 5% to 14% in adults, with the most common manifestation as the red man syndrome associated to nonspecific histamine release.[51] The risk of an adverse reaction to vancomycin increases with concurrent use of narcotics because of non-IgE-mediated, direct release of histamine from mast cells.[52] Although red man syndrome can be treated with slow infusions, IgE-mediated hypersensitivity reactions resistant to slow infusions have been described in which desensitization has been done.[51] A series of seven patients with serious staphylococcal infections resistant to β-lactams antibiotics underwent rapid continuous intravenous infusion with multiple small increases in vancomycin concentration with a syringe pump similar to the protocol described in **Tables 1** and **2**, without major side effects.[52]

IgE-mediated hypersensitivity reactions to quinolones have been reported with cross-reactivity among ciprofloxacin and levaquin. A 35-year-old woman with chronic granulomatous disease and *Burholderia cepacia* infection was desensitized to intravenous ciprofloxacin with no side effects, and the treatment was continued for 4 weeks uneventfully.[53]

Table 1
Rapid intravenous desensitization to 1 g of ceftazidime in a cystic fibrosis patient

Full Dose	1000.0 mg	mg/ml	Total mg to be Injected in Each Bottle
Solution 1	250 cc	0.040	10.000
Solution 2	250 cc	0.400	100.000
Solution 3	250 cc	3.969	992.130

Table 2
Steps for protocol shown in Table 1

Step	Solution	Rate (cc/h)	Time (min)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2	15	0.0200	0.0200
2	1	5	15	0.0500	0.0700
3	1	10	15	0.1000	0.1700
4	1	20	15	0.2000	0.3700
5	2	5	15	0.5000	0.8700
6	2	10	15	1.0000	1.8700
7	2	20	15	2.0000	3.8700
8	2	40	15	4.0000	7.8700
9	3	10	15	9.9213	17.7913
10	3	20	15	19.8426	37.6339
11	3	40	15	39.6852	77.3191
12	3	75	186	922.6809	1000.0000
		Total time =	351 minutes		

DESENSITIZATION TO ASPIRIN AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Asperin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs) include ibuprofen, indomethacin, sulindac, naproxen, tolmetin, fenoprofen, meclofenamate, ketoralac, etololac, oxaprozin, diclofenac, ketoprofen, flurbiprofen, piroxicam, nabumatone, and mefenamic acid, among others. Up to 20% of asthmatic patients develop broad ASA and NSAID intolerance manifested by upper and lower pulmonary symptoms

Table 3
Antibiotic desensitizations performed at Brigham and Women's Hospital 2005 to 2006 using the protocol from Tables 1 and 2

Antibiotic	No. of Desensitizations
Ancef	1
Ceftaxidime	7
Ceftriaxone	4
Cefazolin	1
Ciprofloxacin	1
Ertapenem	1
Imipenem	9
Meropenem	1
Nafcillin	3
Penicillin	7
Piperacillin	3
Trimethoprim	1
Zosyn	3
TOTAL	42

There were no deaths or anaphylactic events during desensitization. Only mild side effects were observed (ie, pruritus, flushing). All patients completed the desensitization protocol, reached the target dose, and were able to receive the prescribed antibiotic course.

(asthma, rhino-conjunctivitis). Nonasthmatic patients can present cutaneous symptoms with chronic urticaria and angioedema when exposed to ASA and NSAIDS, and specific allergic reactions induced by one NSAID or ASA are also described, including anaphylaxis.[54] Desensitization to aspirin is considered in cardiac patients, asthmatic patients with recurrent polyps, and females with antiphospholipid syndromes during pregnancy.

Desensitization to ASA and NSAIDs has been performed to provide cardiac protection and anti-inflammatory treatment in intolerant patients with no alternative medications. Desensitization was initiated in 1927 by Widal[55] with the administration of small daily doses of ASA to ASA-intolerant asthmatic patients until toleration was achieved (**Table 4**). A refractory period was initially observed after a respiratory reaction induced by indomethacin, and tolerance to ASA was induced after a positive oral aspirin challenge.[56] Although the mechanism of desensitization is unknown, desensitized patients tolerate ASA and NSAIDs at pharmacologic doses, and prolonged desensitization can be achieved by daily administration of ASA or NSAIDs.[57] Protocols for ASA and NSAID desensitization are based on the controlled progressive administration of incremental doses starting at 30 mg of ASA and progressing to 60 mg, 100 mg, 150 mg, 325 mg, and 650 mg at 90-minute intervals, as described in the recent Practice parameters.[58] Respiratory responses are measured by forced expiratory volume in 1 second, and a decline of 15% is considered a positive challenge. The dose is then repeated until no reaction occurs and the patient continues until reaching 325 mg or 650 mg. Cross-desensitization is universal for all NSAIDs once desensitization has been achieved at therapeutic levels.[59] Patients who have severe gastrointestinal intolerance to ASA and NSAIDs have been challenge with lysil-aspirin, either nasally or bronchially.[60] Desensitization has been less successful for intolerant patients with cutaneous reactions.[61] Twenty-two patients with urticarial reactions induced by ASA and NSAIDs were desensitized to ASA and tolerated other NSAIDs after ASA desensitization was maintained with daily doses of 325 mg. A study of 11 cardiac patients with a history of acute urticaria/angioedema after ASA and NSAIDs indicated that 9 were able to be desensitized with a fast protocol using incremental ASA doses at 15 to 30 minute intervals (**Table 5**).[62] Similar protocols have been used to desensitized cardiac patients undergoing stent placements.[63]

Long-term ASA Desensitization

Sixty-five ASA-sensitive patients with asthma were desensitized from 1988 to 1994.[64] Increasing oral doses of ASA, up to 650 mg, were administered and daily doses

Table 4
Desensitization to aspirin in an asthmatic patient

Time (min)	Dose (mg)
0	4
90	40
180	81
240	162
330	325
420	650

Aspirin to be continued at 650 mg by mouth twice daily.

Data from White AA, Stevenson DD, Simon RA. The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. Ann Allergy Asthma Immunol 2005;95(4):330–5.

Table 5
Desensitization to aspirin in a patient with aspirin-related urticaria-angioedema

Time (min)	Dose (mg)
0	0.1
20	0.3
40	1
60	3
80	10
100	30
120	40
140	81
160	162

Aspirin to be continued at 162 mg once per day.
Data from Wong JT, Nagy CS, Krinzman SJ, et al. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. J Allergy Clin Immunol 2000;105(5):997–1001.

ranging from 350 mg to 1,950 mg, with a mean of 1,214 mg, were used for 1 to 6 years. These patients presented a significant reduction in the number of sinus infections and asthma hospitalizations, an improvement in the sense of smell, and a decrease in prednisone treatments. A significant reduction in the number of sinus and polyp operations and the use of nasal corticosteroids was also found. Desensitization and maintenance of daily ASA is recommended in patients who have failed medical treatment and have undergone multiple surgeries for polyps or sinusitis.[65] The administration of leukotriene inhibitors during desensitization helps shift the response to the upper respiratory tract without blunting the response.[66] Four pregnant woman with antiphospholipid syndrome were desensitized orally to aspirin with few side effects and were maintained several months on aspirin.[67]

DESENSITIZATION TO CHEMOTHERAPY AND MONOCLONALS

All chemotherapy agents can cause hypersensitivity reactions[68] and those reactions have limited the used of critical drugs in very sick patients for fear of inducing a more severe reaction and possibly death.[69] The choice of an alternative chemotherapy regimen is often limited by tumor sensitivity and, because of the increasing number of cancer survivors, patients are exposed to multiple courses of the same or similar chemotherapy agents. Increased exposures lead to sensitization and to hypersensitivity reactions in an increasing patient population.[70] One-third of the patients exposed to seven or more cycles of carboplatin develop hypersensitivity reactions, including anaphylaxis, and deaths have been reported with re-exposure (**Fig. 1**).[71,72] The need to offer first-line therapy after cancer recurrence and to overcome hypersensitivity reactions has been at the core of the desensitization research and clinical developments.[73]

Desensitization to Chemotherapy Drugs Including Taxenes and Platins

Protocols for the desensitization of hypersensitivity reactions to chemotherapy drugs have been used with success,[19,74–79] but side effects have been prominent and no outcome measurements have been available. Based on in vitro and in vivo data generated in the author's division,[16] a standardized three-solution, 12-step protocol was

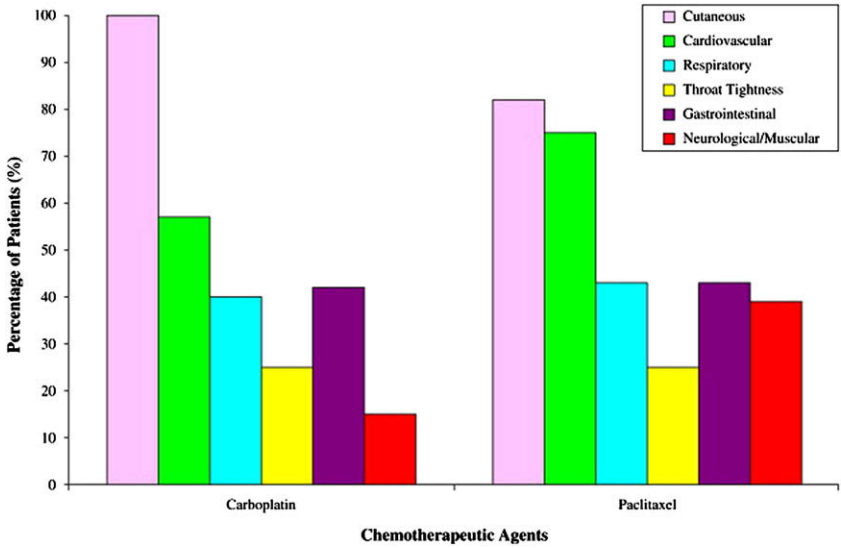

Fig. 1. Frequency of symptoms and signs during initial hypersensitivity reactions. (*From* Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122(3):578; with permission.)

generated that allowed for gradual increases in the infusion rate and drug concentration, infusing the target dose over 5.8 hours, as seen in **Tables 6** and **7**. Three solutions—A, B, and C, containing X/100 mg, X/10 mg, and X mg, respectively, diluted in 250 mL of D5 water—were used in sequence of increasing concentrations. The concentration of solutions A, B, and C were (X/100)/250, (X/10)/250, and (X)/250 mg/mL, respectively. Solution A was used for steps 1 to 4, Solution B for steps 5 to 8, and Solution C for steps 9 to 12. The rate of the infusion was changed every 15 minutes, with each step delivering approximately twice the dose of the previous step. The final step 12 maintained a constant rate of infusion to deliver the remainder of the total dose. One-on-one care (nurse/patient ratio) was provided for each desensitization, and nurses were trained by the allergy team on how to administer the protocol and how to recognize the symptoms of hypersensitivity reactions.

Table 6
Standard desensitization protocol using a total dose of 500 mg as an example

Total Dose	500 mg	Solution Concentration	Total Dose in Each Solution (mg)
Solution A	250 mL	0.02 mg/mL	5.0[a]
Solution B	250 mL	0.20 mg/mL	50.0[a]
Solution C	250 mL	2.00 mg/mL	500.0[a]

[a] The sum of the doses in Solutions A, B, and C equals 555 mg. Total dose infused is 500 mg.

Data from Lee CW, 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.

Table 7
Steps for protocol used in Table 6

Step	Solution	Rate (ml/h)	Time (min)	Administered Dose (mg)	Cumulative Dose Infused (mg)
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500.000
			Total time = 5.82 h		Total dose infused = 500 mg

Data from Lee CW, 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.

Once a patient completed a successful course of desensitization, all subsequent repeated courses of chemotherapy were given in the out-patient facility with a desensitization-trained chemotherapy nurse in one-to-one attendance. The volumes of the bags were adjusted for time constraints to100 mL of D5 water.

Rapid Desensitization for Hypersentivity Reactions to Taxenes

Paclitaxel is a widely used antineoplastic agent with activity against ovarian, breast, and other solid tumors. It was initially isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) in the 1970s, and its antimitotic activity is a result of the bundling of microtubules, which arrests cell division. Docetaxel is a semisynthetic taxane originally extracted from the needles of the European yew tree (*Taxus baccata)*, whose antimitotic activity is similar to that of paclitaxel.[80]

A high incidence of hypersensitivity reactions (HSRs) were observed with paclitaxel in early clinical trials, involving flushing, hemodynamic changes, dyspnea, musculoskeletal pain, paresthesias, and gastrointestinal symptoms, with fatalities reported. Symptoms frequently occurred during the first course of therapy, within seconds to minutes of beginning the infusion, indicating a lack of need for prior sensitization.[13] Slower infusion rates and premedication with H1, H2 antihistamine receptor antagonists, and corticosteroids have decreased the incidence of HSRs to less than 10%.[81] Despite those interventions, there is a subset of patients with taxene-responsive cancers who present HSRs, in whom rapid desensitization is indicated.[80] Attempts at using docetaxel in patients with paclitaxel HSRs have not proven universally successful.[49] HSRs to taxenes resemble anaphylactic reactions induced by the acute release of mast cell/basophil mediators, but skin tests have been negative, indicating that the diluent cremophor or the generation of reactive metabolites capable of activating complement or directly mast cells/basophils may be responsible.[29]

The author used a standard desensitization protocol developed at the Brigham and Women's Hospital to desensitize 40 patients who presented a hypersensitivity reaction after the first or second infusion of paclitaxel or docetaxel for a total of 176 desensitizations.[7,49,82] The limited infusion times avoids neutropenia. The most prominent presenting symptoms of hypersensitivity to taxenes included flushing, pruritus, urticaria, chest pain, hypotension and hypertension, loss of consciousness, gastrointestinal symptoms, musculoskeletal pain, and dyspnea with O_2 desaturation. The initial HSR reactions in those patients were immediate (less than 10 seconds) to a maximum of 15 minutes, with one patient reporting urticaria during 2 weeks following her initial HSR. Readministration at a slow infusion rate, after additional antihistamines and corticosteroids, failed in four patients. One patient, switched to docetaxel, developed a similar HSR, indicating that the vehicle for paclitaxel, cremophor, was not responsible for the HSR reaction. The solutions and protocols for the desensitization protocol are described in **Tables 6** and **7**.

Administration time for all desensitizations ranged from 4 to 8 hours. All 40 patients were successfully desensitized and had repeated desensitizations, completing their chemotherapy cycles. Breakthrough reactions occurred in 12% of the desensitizations and the reactions were less severe than the initial reaction and did not preclude the completion of any treatment course. We noted that the incidence of allergic disease (seasonal allergic rhinitis, asthma, allergy to other drugs, venom sensitivity) was 57%, which far exceeds the 15% to 20% reported for the general population.[83] An earlier review of 19 patients with paclitaxel-induced HSRs found a statistically significant difference in the rate of hymenoptera venom sensitivity, but not other types of allergy, in patients with HSRs when compared with control patients.[84] Patients with allergic conditions seem to be at higher risk for HSRs to taxanes.

Rapid Desensitization for HSRs to Platins

Carboplatin is an effective and well-tolerated cytotoxic agent used as standard front-line chemotherapy for ovarian cancer.[85] Many patients achieve a clinical complete remission with the platinum-based regimen but later develop recurrent disease within 3 years of diagnosis. For patients with platinum-sensitive recurrent cancer, disease relapsing after at least a 6-month disease-free interval, platinum-based chemotherapy remains the most active regimen. In addition to its clinical effectiveness, carboplatin has a low incidence of toxicity and limited nausea or vomiting with anti-emetic therapy.[86] Therefore, the ability to administer carboplatin safely as front-line therapy and in the relapse setting provides a significant clinical benefit to the patient. Patients treated with multiple courses of carboplatin experience increased incidence of HSRs; these reactions are uncommon during the initial courses, but the incidence of reactions increases to 27% in patients receiving more than seven cycles of carboplatin.[87,88] Thus, most cases of carboplatin HSR are observed during the retreatment for relapsed disease. Symptoms of HSR vary from cutaneous reactions, such as flushing and urticaria, to life-threatening respiratory and cardiovascular compromise, including bronchospasm, chest pain, and hypotension, with more than 50% of patients developing at least moderately severe symptoms (see **Fig. 1**).

HSRs to carboplatin are thought to be mast cell/IgE mediated because skin tests performed on the volar surface of the forearm with a drop of a nonirritating concentration of carboplatin at 1 mg/mL to 10 mg/mL is positive in over 80% of reactive patients.[71,89] Eliminating carboplatin as a treatment option presents a significant disadvantage, but death from reintroduction of platinums has been described.[69] Several protocols for reintroduction of carboplatin and other platinums have been developed.[90,91] The author and colleagues treated 54 patient for 162 desensitization

Table 8
Characteristics of initial hypersensitivity reactions to chemotherapy

Symptoms	Carboplatin 31 pts *n* (%)	Paclitaxel 22 pts *n* (%)	Docetaxel 1 pt *n* (%)	Trastuzumab 1 pt *n* (%)	Doxorubicin 1 pt *n* (%)	Uromitexa 1 pt *n* (%)
Cutaneous						
Flushing	17 (54.8)	19 (86.4)	1 (100)	—	1 (100)	—
Pruritus	24 (77.4)	1 (4.5)	—	1 (100)	1 (100)	—
Urticaria	9 (29)	1 (4.5)	—	1 (100)	—	1 (100)
Cardiovascular						
Chest pain	8 (25.8)	15 (68.2)	1 (100)	—	—	1 (100)
Tachy/bradycardia	2/1 (9.7)	2/0 (9.1)	—	—	—	—
Hyper/ hypotension	2/2 (12.9)	5/1 (27.3)	—	—	—	—
Lightheadedness	4 (12.9)	4 (18.2)	—	—	—	—
Loss of consciousness	2 (6.5)	4 (18.2)	—	—	—	—
Pulmonary						
Dyspnea	12 (38.7)	10 (45.5)	—	1 (100)	1 (100)	1 (100)
Desaturation	5 (16.1)	7 (31.8)	—	—	—	1 (100)
Gastrointestinal						
Nausea/vomiting	6 (19.4)	1 (4.5)	—	—	—	—
Abdominal pain	5 (16.1)	6 (27.3)	—	—	—	—
Oropharynx						
Throat tightness	3 (9.7)	4 (18.2)	—	1 (100)	—	—
Musculoskeletal						
Back pain	1 (3.2)	10 (45.5)	—	—	—	—

Data from Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. Gynecol Oncol 2005;99(2):393–9.

Table 9
Characteristics of breakthrough reactions occurring during desensitization

	Carboplatin (11 pts)	Paclitaxel (6 pts)	Trastuzumab (1 pt)
Cutaneous			
Flushinig	4	3	1
Pruritus	7	1	1
Urticaria	3	1	1
Cardiovascular			
Chest pain	1	2	—
Tachy/bradycardia	20	1/10	—
Hyper/hypotension	2/1	1/1	—
Pulmonary			
Dyspnea	3	—	—
Desaturation	1	—	—
Gastrointestinal			
Abdominal pain	1	1	—
Oropharynx			
Throat tightness	1	—	1

Data from Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. Gynecol Oncol 2005;99(2):393–9.

courses with the standardized desensitization protocol described in **Tables 6** and **7**, the same as for taxene desensitizations with three solutions for 6 hours and 12 steps.[7] Positive skin test for the initial patient series was positive in 80.8% of 21 initial patients. Patients received a median of eight courses before developing their initial hypersensitivity reaction. Most patients had reactions during their second-line therapy for recurrent cancer. Typically after recurrence of their disease, patients were re-exposed to carboplatin during the seventh cycle and develop reactions during the eighth cycle. This observation suggests that a prolonged period of sensitization is required before the onset of HSR. The reaction profile was consistent with type I HSRs (see **Fig. 1**) and included flushing, pruritus, urticaria, nausea, dyspnea, tachycardia, hypertension or

Table 10
Effect of desensitization on skin test reactivity: wheal/flare (mm) response for patient 10

	Controls		Carboplatin	
	Histamine (Prick)	Diluent (Intradermal)	10 mg/mL (Intradermal)	Wheal Ratio[a]
Before desensitization	Positive (5/15)	Negative (4/0)	Positive (8/15)	1.6
After desensitization	Positive (4/13)	Negative (4/0)	Negative (4/1)	1

[a] Wheal produced by carboplatin (intradermal) versus wheal produced by histamine (prick).
Data from Lee CW, 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.

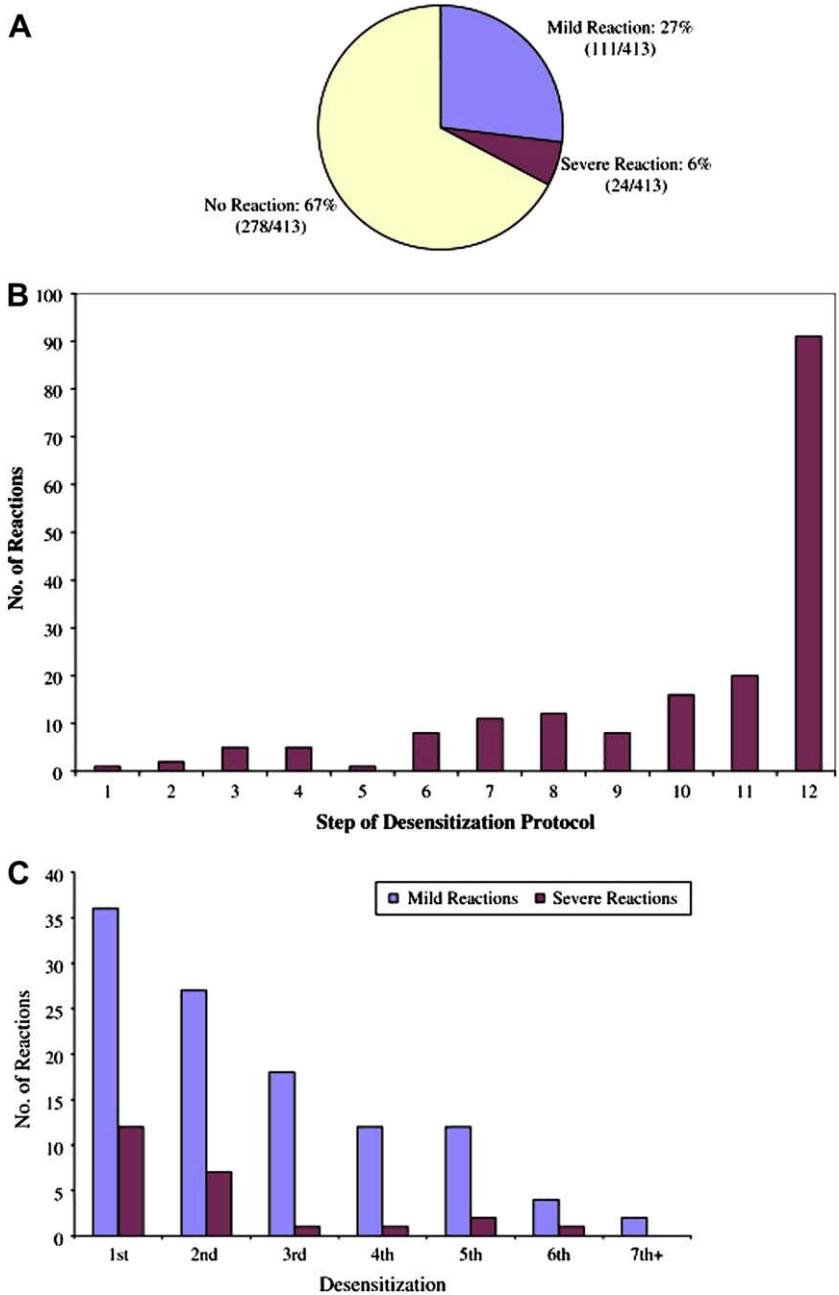

Fig. 2. (*A*) Number and severity of reactions during desensitization. A mild reaction was defined as absence of chest pain, changes in blood pressure, dyspnea, oxygen, desaturation, or throat tightness. A severe reaction included one of these. (*B*) Desensitization step at which reactions occurred (total number of reactions = 180). (*C*) Desensitization course at which reactions recurred (total number of reactions = 135, of which 111 were mild and 24 were severe). (*From* Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122(3):579; with permission.)

hypotension, and chest pain. Most patients had their initial HSR during the infusion, with six patients experiencing symptoms within 15 minutes of infusion, but no delayed reactions were observed. Cutaneous manifestations were present in 96% of the patients and extracutaneous symptoms were present in 77% of the patients, including hypotension and loss of consciousness (**Table 8**). In contrast, with patients presenting reactions to paclitaxel, there was a low incidence of musculoskeletal pain, including back pain (3% versus 45%, see **Table 8**). All patients successfully received all planned courses of carboplatin though the desensitization program. Breakthrough reactions occurred in 12% of the desensitizations, with mild reactions, none of which resulted in cardiovascular collapse or death (**Table 9**). To determine the effect of desensitization on cutaneous mast cell reactivity, a skin test was performed before and after desensitization. The result of the skin test to carboplatin was positive before desensitization but became negative after the infusion (**Table 10**), demonstrating the inhibition of cutaneous mast cell reactivity, consistent with other studies (**Fig. 2**).[71]

Rapid Desensitization for Biologic Agents and Monoclonal Antibodies

HSRs to humanized monoclonal antibodies are rare but their frequency is increasing as increased cancer and rheumatologic patients are exposed to multiple courses. Patients with HSR to rituximab (Rituxan) have been described to trastuzumab (Herceptin), and to anti-TNFα monoclonal antibodies.[92–95] In patients with reactions compatible with a hypersensitivity type I, in whom an IgE/mast cell mechanism can be demonstrated, desensitizations have been reported for humanized monoclonal antibodies.[96] The author and colleagues used the protocol described in **Tables 11** and **12** to desensitize patients to rituximab and trastazumab.[7,8] The initial reaction was severe in both cases and included anaphylaxis. An IgE mechanism was demonstrated by positive skin test to nonirritant concentrations of the drugs. Breakthrough symptoms were less severe than the initial reaction and allowed the patients to complete their courses. Patients received their first desensitization in the intensive care setting and for repeated desensitizations were transitioned to the out-patient clinics with one-on-one nurse support. One patient desensitized to trastazumab presented side effects during the first two initial desensitizations and was later transitioned to the out-patient setting, where she underwent eight more courses without side effects, with a modified protocol.

Outcomes of Desensitizations and Cancer Progression

The author and colleagues did a safety study in the largest series of chemotherapy and monoclonal antibodies desensitizations, providing safety data for 413 cases. Drugs included carboplatin, cisplatin oxaliplatin, paclitaxel, liposomal doxorubicin, and rituximab. Of the subjects in the study, 94% presented mild or no reactions and only 6%

Table 11
Desensitization protocol for rituximab IV (851 mg): solution preparation

	Volume (mL)	Concentration (mg/mL)	Total Amount of Drug in Each Solution (mg)
Solution 1	250	0.034	8.510
Solution 2	250	0.340	85.100
Solution 3	250	3.377	844.303

Amount of drug prepared exceeds dose of drug delivered during desensitization because solutions 1 and 2 are not completely infused. A full dose is 851 mg of rituximab.

Table 12
Desensitization protocol for rituximab IV (851 mg): protocol for administration

Step no.	Solution no.	Rate (mL/h)	Time (min)	Volume Infused Per Step (mL)	Administered Dose (mg)	Cumulative Dose (mg)
1	1	2.0	15	0.50	0.0170	0.0170
2	1	5.0	15	1.25	0.0426	0.0596
3	1	10.0	15	2.50	0.0851	0.1447
4	1	20.0	15	5.00	0.1702	0.3149
5	2	5.0	15	1.25	0.4255	0.7404
6	2	10.0	15	2.50	0.8510	1.5914
7	2	20.0	15	5.00	1.7020	3.2934
8	2	40.0	15	10.00	3.4040	6.6974
9	3	10.0	15	2.50	8.4430	15.1404
10	3	20.0	15	5.00	16.8861	32.0264
11	3	40.0	15	10.00	33.7721	65.7986
12	3	75.0	186	232.50	785.2014	851.0000

Total time = 351 minutes (5.85 hours).

presented reactions that required antihistamines or steroids. No epinephrine was used in any case and no deaths occurred. All patients received their treatment courses after the initial desensitization. The majority of the reactions occurred during step 12, when patients were receiving the drug at the maximal rate and full concentration. When desensitizations were repeated, the side effects were less frequent and less severe, because of additional steps added before the step at which the patient reacted or was given additional antihistamines. The addition of antileukotriene therapy and prostaglandin blockade with aspirin seems to improve the side effects over the use of steroids.[97]

Whether chemotherapy desensitizations are effective at tumor killing or control needs to be defined. In a small population of 26 patients receiving carboplatin desensitization for recurrent cancer, 10 (38.5%) had a radiographic response (partial or complete response) or a greater than 50% drop of initial CA125 value, 11 (42.3%) had stable disease radiographically or CA125 response (<50% drop), and 5 (19.2%) had progressive disease after 1 to 2 cycles of carboplatin. Of the three patients receiving paclitaxel desensitization for recurrent cancer, one had clinical response to therapy, one had stable disease, and one had progressive disease. Of 16 patients receiving paclitaxel desensitization for newly diagnosed cancer, 16 patients (100%) achieved clinical remission. Those are the expected rates for cancer patient populations not receiving chemotherapy desensitizations.

SUMMARY

Rapid desensitization protocols are available to patients who present with IgE and non-IgE-dependent hypersensitivity to drugs, including anaphylaxis to antibiotics, chemotherapy, monoclonals, aspirin, and other drugs. Typical hypersensitivity symptoms include pruritus, flushing, urticaria, angioedema, respiratory and gastrointestinal distress, and changes in blood pressure, including hypotension and shock. Associated musculoskeletal symptoms and back pain can be present in patients reacting to taxenes and monoclonal antibodies. During rapid desensitization, drug antigens

are reintroduced in an incremental fashion, allowing for full therapeutic doses to be delivered with minor or no side effects. Temporary toleration is achieved in hours and can be maintained if drug antigens are administered at regular intervals, depending on pharmacokinetic parameters. Desensitization should only be done in settings with one-on-one nurse-patient care and where resuscitation personnel and resources are readily available. After a successful desensitization, repeated desensitizations can be done in outpatient or inpatient settings with similar conditions for patients on chemotherapy of monoclonal therapies. This provides flexibility and allows patients to remain in clinical studies. Breakthrough symptoms during desensitization are less severe than the initial HSR and deaths have not been reported in the last 5 years. Managing breakthrough symptoms with antihistamines and steroids and decelerating the dose escalation with intermediate infusion steps successfully improves the tolerability of desensitization protocols. Blocking leukotrienes and prostaglandins has improved side effects. Reactions occurring days to weeks after drug treatment, such as serum sickness, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis may not be considered for desensitization protocols.

Education of nurses, pharmacists, and oncology and allergy specialists will lead to the judicious use of desensitization protocols for patients with hypersensitivity reactions in need of first-line therapy. Basic research is needed to uncover the cellular and molecular mechanisms underlying the temporary toleration induced by desensitization, so that pharmacologic interventions can improve its safety and efficacy. From the outcomes and safety data gathered, it appears that a flexible 12-step protocol could be universally used for all drug desensitizations.

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