REVIEWS

Rapid Drug Desensitization for Hypersensitivity Reactions to Chemotherapy and Monoclonal Antibodies in the 21st Century

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■ **Abstract**

The frequency of hypersensitivity reactions (HSR) to drugs has risen in the last 10 years owing to increased exposure to better and more allergenic medications including monoclonal antibodies. HSRs prevent patients from using their first-line therapy, leading to decreased quality of life and life expectancy. Although premedication with antihistamines, leukotriene blockers, and corticosteroids can protect against mild-to-moderate HSR, none of these medications has provided protection against anaphylaxis. Rapid drug desensitization is a treatment option for patients with HSR to their first-line medication that protects against anaphylaxis. Although the mechanisms of drug desensitization are not completely understood, in vitro mast cell models of IgE antigen desensitization have led to the design of safe and effective in vivo protocols aimed at protecting highly sensitized patients from hypersensitivity reactions and anaphylaxis. This review provides an insight into the mechanisms of IgE/mast cell desensitization, the principles and practice of drug desensitization, and an overview of the different desensitization protocols and their safety and efficacy profiles. Drug desensitization should only be performed by allergists, trained nurses, and experienced pharmacists, since this high-risk procedure involves reintroducing allergenic medication to highly sensitized patients, with the consequent potential for severe or fatal HSRs.

Key words: Desensitization. Drug hypersensitivity. IgE-mediated. Chemotherapy. Monoclonal antibodies.

■ **Resumen**

Las reacciones de hipersensibilidad a medicamentos han aumentado en los últimos 10 años debido a la exposición prolongada por parte de los pacientes a mejores medicamentos diana con más potencial alergénico, incluyendo los anticuerpos monoclonales. Estas reacciones impiden que los pacientes puedan ser tratados con medicamentos de primera línea disminuyendo la calidad y expectancia de vida. El uso de pre medicaciones para evitar estas reacciones, incluyendo los anti-histamínicos, los bloqueantes de leukotrienos y los esteroides son capaces de proteger a pacientes con reacciones moderadas pero no protegen contra reacciones anafilácticas. En cambio la desensibilizacion a medicamentos es capaz de proteger contra la anafilaxia al mismo tiempo que provee a los pacientes con la medicina más adecuada para su tratamiento. Aunque los mecanismos de la desensibilización no están totalmente esclarecidos existen modelos celulares in vitro y modelos de roedores in vivo basados en la desensibilización IgE de mastocitos que han permitido establecer las bases y principios de la desensibilización y proveer protocolos in vivo para proteger a los pacientes altamente sensibilizados de reacciones de hipersensibilidad y anafilácticas. Esta revisión intenta proveer informacion acerca de los avances en los mecanismos de desensibilización, los principios y la práctica de las desensibilizaciones, los diferentes protocolos con los datos de eficacia y seguridad basadas en evidencia. Las desensibilizaciones a medicamentos solo pueden ser proveídas por alergólogos, enfermeras entrenadas y expertos farmacéuticos/as puesto que son tratamientos de alto riesgo en los cuales pacientes altamente sensibilizados son expuestos a la medicinas a las cuales están sensibilizados, con el consecuente riesgo de reacción de hipersensibilidad severa o fatal.

Palabras clave: Desensibilizacion. Hypersensibilidad a medicamentos. IgE mediada. Quimioterapia. Anticuerpos monoclonales.

Rapid Drug Desensitization in the 21st Century

Today, patients with cancer and chronic inflammatory diseases are repeatedly exposed to new, more powerful, and targeted chemotherapy drugs and monoclonal antibodies with the potential for sensitization and induction of hypersensitivity reaction (HSR) [1]. In the last 10 years, the considerable increase in the frequency of HSR to drugs has led to the emergence of new treatment modalities for allergic patients for whom first-line therapies would be preferred [2]. In this group, first-line therapy can increase quality of life and life expectancy. Typically, HSRs include cutaneous manifestations such as flushing, pruritus, urticaria, and angioedema [3]. More severe reactions include cardiovascular manifestations (eg, chest pain, tachycardia, a sense of impending doom, presyncope, syncope, and hypotension) and respiratory symptoms (eg, sneezing, nasal congestion, dyspnea, coughing, wheezing, and oxygen desaturation). Severe reactions can also be characterized by throat tightness and gastrointestinal complaints, including nausea, vomiting, diarrhea, and abdominal pain [4]. Less common signs and symptoms include neuromuscular symptoms, such as visual changes, back, chest, and pelvic pain, and numbness/weakness, or, in some cases, fever and chills [5]. The evaluation of patients who experience HSR includes categorization of reactions as mild (cutaneous symptoms), moderate (cutaneous, respiratory, and gastrointestinal involvement), and severe (changes in vital signs, syncope, seizures, and cardiac or respiratory arrest) [6]. Tryptase levels measured at the time of the HSR are key to understanding the mechanism of the reaction and its severity [7]. During chemotherapy, HSR tryptase levels can increase 2- to 5-fold the normal range, thus indicating systemic mast cell degranulation through IgE and non-IgE mechanisms [8]. Skin testing is used to assess the involvement of IgE in the reaction [9], and blood-specific IgE for platins has recently demonstrated its value in assessing patients who react to platins and uncovering cross-reactivity between carboplatin, cisplatin and oxaliplatin [10] (Figure 1).
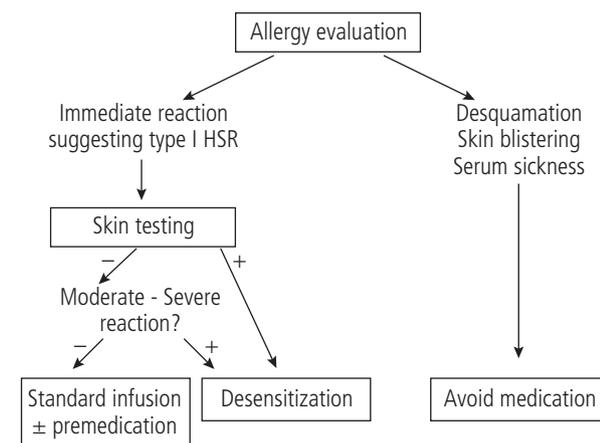
Once a patient has presented an HSR, re-exposure of IgE- and non–IgE-sensitized patients to their allergenic medication can lead to the sudden systemic release of inflammatory mediators from activated mast cells and/or basophils, thus inducing HSRs and, in severe cases, anaphylaxis [11]. Avoiding medication can effectively circumvent HSR, although it can lead to significant morbidity and mortality due to suboptimal treatment of disease. Rapid drug desensitization (RDD) is a treatment modality by which mast cells are rendered hyporesponsive, thus protecting patients against anaphylaxis [12]. Desensitization protocols have been developed to help deliver full therapeutic doses of drug allergens in an incremental, stepwise fashion without eliciting life-threatening symptoms [13]. IgE- and non–IgE-sensitized patients can present with similar symptoms and elevated serum tryptase levels, indicating that mast cells and/or basophils are the cellular targets of these reactions. For IgE-sensitized patients, reactivity to skin testing is abolished by desensitization, thus implying inhibition of the mechanisms that induce mast cell activation [14].

Mast cell activation results from antigen cross-linking of IgE-bound FcεRI receptors, which results in their aggregation and the recruitment and activation of target molecules, calcium mobilization, degranulation, arachidonic acid metabolism, and cytokine and chemokine gene transcription [15]. In vitro and in vivo mouse models of rapid mast cell/IgE desensitization (Figure 2) have provided evidence that increasing doses of antigen delivered at fixed time intervals induced highly specific and prolonged hyporesponsiveness to triggering doses of the desensitizing antigen [16]. Mast cells desensitized to dinitrophenyl (DNP) or ovalbumin (OVA) antigens were able to almost completely inhibit release of β-hexosaminidase and preformed TNF-α, calcium flux, and arachidonic acid metabolism with reduced generation of leukotrienes and prostaglandins, suggesting complete abolition of the acute phase of mast cell activation [17] and indicating that subclinical release of mediators is unlikely during desensitization in humans. Desensitized mast cells did not release significant amounts of newly generated IL-6 or TNF-α, indicating a lack of late phase release of mediators. This may explain that during rapid desensitizations few patients had delayed reactions. Delayed reactions were not anaphylactic, possibly owing to the lack of generation of late phase mediators [17]. When mast cells were sensitized to both DNP and OVA antigens, DNP-desensitized cells responded fully to OVA and vice versa, proving antigen specificity and providing evidence that the activating signal transduction pathways are not exhausted during rapid desensitization [17]. Internalization of antigen-specific IgE bound to the α chain of FcεRI was decreased after rapid desensitization [18], indicating that the lack of reactivity during desensitization was not due to the complete disappearance of surface IgE and FcεRI when bound to small doses of antigen (Figure 2) or disappearance of Syk [19]. In vitro and recent animal studies [18] provided evidence of the abrogation of early- and late-phase activation events. This evidence formed the basis for the generation of safe human RDD protocols successfully used in hundreds of desensitizations, illustrating profound inhibition of mast cell responses and protection against anaphylaxis [20].
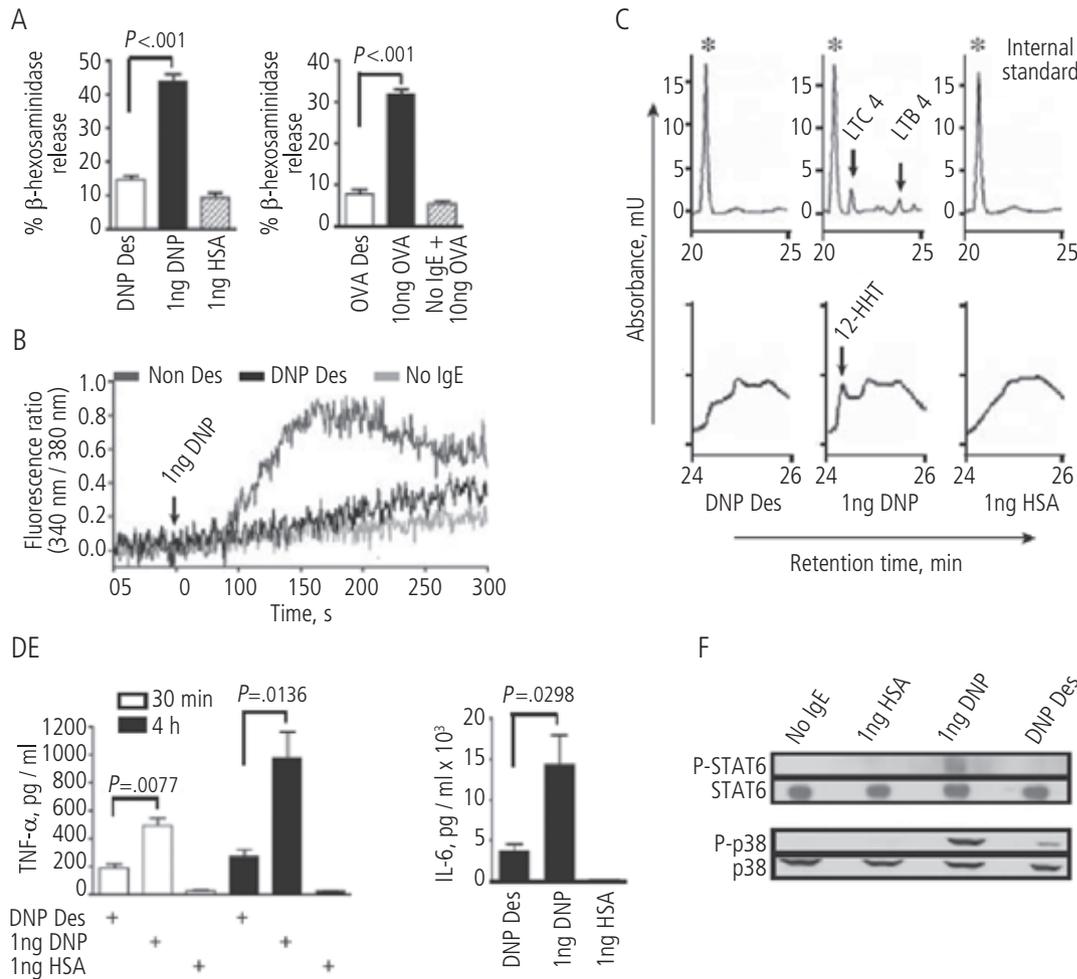

Figure 1. Algorithm for the assessment and treatment of patients with hypersensitivity reactions to chemotherapy and monoclonal antibodies. Adapted from Brennan et al [41].

Figure 2. Rapid desensitization impairs early- and late-phase responses to mast cell activation. A, Percentage of β-hexosaminidase release after desensitization (DNPDes or OVADes) or challenge with DNP-HSA or OVA (1 ng DNP or 10 ng OVA) and negative control HSA. B, Calcium flux when 1 ng DNP-HSA is added to cells treated as indicated. C, Reverse phase high-performance liquid chromatography analysis of arachidonic acid products (LTC4 and LTB4) in the supernatants of cells treated as indicated. D and E, Secretion of TNF-α and IL-6 from mast cells during the early phase (30 minutes) and late phase (4 hours). F, STAT-6 phosphorylation during antigen activation and during rapid desensitization. Adapted from Sancho-Serra et al [17].

Clinical Rapid Desensitization: Protocols and Agents

The Brigham and Women's Desensitization Program generated a flexible 12- to 20-step protocol, which rendered mast cells unresponsive by delivering x2 to x2.5 doses of drug antigens at fixed time intervals starting at 1/1000 to 1/100 dilutions of the final concentration [21]. The most commonly used protocol is based on 3 bags and 12 steps, with 3 x 10-fold diluted solutions at escalating rates (Figure 3). Patients with severe HSRs and anaphylactic reactions are desensitized with 16 steps (4 bags) or 20 steps (5 bags). Other protocols have been successfully used by other groups, and shorter protocols with only 2 bags have been proposed for patients with a mild-to-moderate risk [22,23]. These new protocols are empiric and not based on in vitro or animal data, and their success may depend on the target patient population. They should be used with extreme caution in highly sensitized patients, since in vitro data suggest

Figure 3. The standard 12-step, 3-bag desensitization protocol from the Brigham and Women's Desensitization Program (adapted from Castells et al [21]).

that the small doses of antigen delivered during the early phase of the desensitization provide the platform for further doses and enable the target dose to be reached [17].

Desensitization to Taxanes

Paclitaxel and docetaxel are widely used in the treatment of ovarian, breast, non-small cell lung, and other solid tumors. HSR to these taxanes is common: in early trials of paclitaxel, up to 30% of patients developed acute infusion reactions [24]. Premedication with antihistamines and corticosteroids and slower infusion rates have reduced the rate of severe HSR to less than 10% [25]. Similarly, approximately 30% of patients receiving docetaxel without premedication developed acute hypersensitivity reactions; premedication reduces this rate to less than 10% [1].

Acute reactions to taxanes include typical and atypical symptoms of hypersensitivity, such as dyspnea, urticaria, flushing, back or chest pain, gastrointestinal symptoms, hypotension, hypertension, and erythematous rashes (Figure 4). Symptoms typically develop within the first few minutes of the infusion, and most often occur on the first or second exposure to the drug, indicating prior sensitization or cross-reactivity with other sensitizing medications [26]. The possible mechanisms of taxane infusion reactions include complement activation, direct mast cell and/or basophil activation, and IgE-mediated anaphylaxis. There is evidence that both the taxane moiety and the diluent polyethoxylated castor oil, which is also used as a solubilizing vehicle for cyclosporine and vitamin K, can induce adverse reactions [27]. An albumin–based formulation of paclitaxel has also been implicated in HSRs,

Agents	Number of Infusions Prior to First Reaction	Clinical Manifestations of Hypersensitivity
Platins	6 to 8	Rash, pruritus, flushing, respiratory, cardiovascular
Taxanes	1 to 2	Cutaneous, pain (back, chest, low back)
Biological agents	1 to 2 or multiple	Fever, chills, rash, respiratory, cardiovascular

Figure 4. Typical and atypical symptoms of HSRs to chemotherapy and monoclonal antibodies (from Mezzano et al [12] and Castells et al [21]).

thus providing further evidence that the taxane moiety can be the source of HSRs. Skin testing with paclitaxel can provide evidence of an IgE-mediated mechanism [28]. Desensitization to taxanes is generally well tolerated. In a series of 17 patients who underwent 77 desensitizations to paclitaxel or docetaxel, 72 desensitizations occurred without reactions. During sensitization, 4 patients had a total of 5 reactions, all of which were much less severe than their original reactions. On the other hand, 5 patients who underwent rechallenge (ie, readministration of the culprit taxane by regular infusion) prior to desensitization experienced recurrent reactions despite additional premedication and a reduced infusion rate [29]. Based on this and other data, patients experiencing HSR with involvement of 2 organs should not be re-exposed to the culprit medication with increased premedication, since anaphylaxis is not prevented by increased dosing of corticosteroids.

Desensitization to Platins

Platin-containing compounds are widely used in the treatment of ovarian cancer and other malignancies. Cisplatin was the first to be used, although it was the relatively low toxicity profile of the second-generation agent carboplatin that is largely responsible for the increased popularity of platins during the past decade. The third-generation platinum derivative oxaliplatin is widely administered for the treatment of metastatic colorectal cancer. Increasingly frequent use of platinum-containing compounds has led to an increase in the incidence of HSR: hypersensitivity ranges from 5% to 20% for cisplatin, from 9% to 27% for carboplatin, and from 10% to 19% for oxaliplatin [30,31]. The mechanism of platin hypersensitivity is based on IgE-induced sensitization, and repeated exposures are required. Typically, reactions occur at the time of cancer recurrence when patients have been exposed to at least 6 cycles. In one study, 50% of the initial HSRs to a platin occurred during the eighth course [32]. Likewise, Castells et al [21] found that 40 out of 55 patients with carboplatin HSRs reacted between the seventh and tenth exposures. Cisplatin and oxaliplatin have similar characteristics in that reactions mostly occur between the fourth and eighth courses or after the sixth exposure, respectively [31].

The characteristics of HSRs to platinum agents are typical of type I HSRs, namely, most patients develop cutaneous symptoms with palmar or facial flushing. In addition, reactions may become moderate-to-severe, and cardiac arrest and deaths have been reported (Figure 4) [32,33]. In the report of 413 desensitizations by Castells et al [21], of the 60 patients who had an HSR to carboplatin, 100% had cutaneous symptoms, 57% had cardiovascular symptoms, 40% had respiratory symptoms, and 42% had gastrointestinal manifestations [21]. HSRs to oxaliplatin are often similar to HSRs to carboplatin and cisplatin, although respiratory symptoms are common, and reactions such as Gell and Coombs type II antibody-mediated thrombocytopenia and Gell and Coombs type III immune complex–mediated symptoms of chronic urticaria, joint pain, and associated proteinuria have been reported [34]. Idiosyncratic reactions to oxaliplatin, including cytokine release syndrome with fevers and chills and pulmonary fibrosis, make adverse responses to oxaliplatin heterogeneous and unpredictable [35].

The diagnosis of IgE sensitivity to platinum drugs has been confirmed by skin testing. Of 60 patients referred for previous HSRs to carboplatin, 53 were skin test–positive (Figure 5). Of the 7 patients with negative skin test results, 2 tests became positive after several infusions, 1 skin test was considered delayed positive, and 4 patients experienced HSRs during the infusion [21,38]. Hesterberg et al [36] recently published a report of 38 women with HSR to carboplatin who had undergone skin testing and desensitization. Thirteen patients had negative skin test results with carboplatin, and 7 of those patients had reactions during desensitization. Interestingly, when the patients with negative skin test results were classified according to the time from the HSR to skin testing, those with a recent history of HSR (<3 months) and negative skin test results did not react, whereas all 7 of the reactors had a remote history of HSR (>9 months).

Patients who are hypersensitive to a platinum-containing compound or who have a positive skin test result must not receive the same agent with increased doses of premedication, since deaths have been reported in patients with mild reactions who experienced erythema again but were able to finish the infusions [2]. However, 12 patients with initially severe reactions including hypertension or hypotension were unable to complete subsequent carboplatin infusions despite prophylaxis [37]. Attempts to circumvent a reaction by switching to another platinum-based agent cannot be recommended. One patient died from anaphylaxis in a series of 7 patients who switched from carboplatin to cisplatin [38]. Desensitization has proven to be a safe and effective way to enable a patient to continue carboplatin chemotherapy [39]. Variability in the success rates of desensitization is believed to be due to the heterogeneity of protocols.

Desensitization to Monoclonal Antibodies

HSRs to monoclonal antibodies can occur after first or second exposure or, as in the case of platins, after multiple exposures [40]. Symptoms of HSRs range from typical type I HSR symptoms (flushing and pruritus) to atypical symptoms, such as those seen in cytokine storms (fever, chills, and back pain), and can be severe, sometimes leading to anaphylaxis [21]. The rates of HSRs that are clinically consistent with immediate hypersensitivity to specific monoclonal antibodies have been reported to be 5% to 10% for rituximab, 2% to 3% for infliximab, and 0.6% to 5% for trastuzumab [41]. Immediate HSRs have also been reported for omalizumab, natalizumab, basiliximab, abciximab, and cetuximab. Almost 70% of initial HSRs to monoclonal antibodies include a cutaneous component, the most frequently observed type of reaction overall, followed by cardiovascular and respiratory disorders and throat tightness [40]. The intensity of reactions to monoclonal antibody infusions is variable. Recent studies have reported that 26% of initial reactions are mild, 48% are moderate, and 26% are severe [41].

Patients with a history suggestive of a mast cell–mediated, or possibly IgE-mediated, HSR should undergo skin testing with the offending agent. RDD protocols for most monoclonal antibodies are generated using the principles discussed above (Figure 2). Despite its general success, some patients experience HSRs during RDD. In general, these reactions are less intense than the patient's original reaction. Treatment of such HSRs is aimed at blocking mast cell mediators including histamine, prostaglandins, and leukotrienes [42]. In the event of a reaction during RDD, the infusion is stopped immediately and the reaction is treated. Once the reaction resolves, the protocol can almost always be resumed and completed.

Treatment of Reactions During Desensitization and Overall Safety and Efficacy

In the largest case series of rapid desensitizations reported to date [21], 98 patients with HSRs to chemotherapy underwent 413 desensitizations; 67% of desensitizations had no reactions, and 27% had only mild reactions, even though 77% of patients

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*
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

*Wheal produced by carboplatin (intradermal) versus wheal produced by histamine (prick.)

Carboplatin skin test results

Skin test results	No. of patients, %
Positive (total)	21 (80.8)
Prick, 10 mg/mL	1 (3.8)
Intradermal, 1 mg/mL	12 (46.2)
Intradermal, 10 mg/mL	8 (30.8)
Negative	5 (19.2)

Figure 5. Skin testing for carboplatin and effect of desensitization (adapted from Lee et al [38] and Castells et al [21]).

had experienced a severe initial HSR. Despite the fact that the remaining 6% of desensitizations were characterized by severe HSRs, epinephrine was only administered during 1 desensitization, and there were no deaths. All patients in the case series were able to receive their full target dose. In their case series of 105 desensitizations to monoclonal antibodies in 23 patients, Chung and O'Neil [40] found that 74% of the initial HSRs were moderate-to-severe. During desensitization, reactions were observed in 29% of desensitizations, and 90% of these were mild.

In the large series reported by Castells et al [21] (413 desensitizations in 98 patients), there were a total of 180 reactions, all of which subsided when treated appropriately after stopping the infusion [21]. Most reactions (75%) occurred during infusion of solution 3, and 51% of reactions occurred during step 12 of the desensitization protocol (Figure 5). The frequency and severity of the reactions decreased with repeated desensitizations. A similar rate of reactions (29%) was reported for monoclonal antibodies [40,41], cutaneous reactions were the most common, and, again, most reactions (70%) occurred during step 12. Treatment of reactions during desensitization is based on blocking local and systemic effects of mast cell mediators (including histamine, prostaglandins, and leukotrienes) [40,41], pausing the infusion, and administering either diphenhydramine or hydroxyzine (25-50 mg administered intravenously) and/or ranitidine (50 mg administered intravenously). Methylprednisolone sodium succinate (0.5 mg/kg administered intravenously) can be used in severe reactions, and epinephrine 0.3 mL (1 mg/mL) should be available at the bedside. On resolution of the reaction, the protocol can be resumed from the step at which it had been paused. For future desensitizations, administration of additional premedications or administration between specific steps is recommended, and adding or lengthening steps before the step at which a reaction occurs is also appropriate. This second component is used only when a patient reacts despite additional premedication. By using this approach, we have been able to markedly reduce the rate of reactions over multiple successive desensitizations (Figure 6).

A subset of patients continue to react during desensitization despite protocol modification and addition of high-dose histamine receptor blockade and corticosteroids. These patients respond to prophylaxis with oral acetylsalicylic acid 325 mg and oral montelukast 10 mg. In the study by Breslow et al [42], 78 desensitizations were performed in 14 patients with HSR to platinum chemotherapy who had cutaneous symptoms, many also with associated systemic reactions, during RDD. Pretreatment with acetylsalicylic acid and montelukast 2 days before and on the day of RDD enabled 86% of the patients to tolerate subsequent desensitizations with a less severe or no HSR (Figure 7). Interestingly, only 62% of patients in a control group that received adjunctive premedication with methylprednisolone were able to tolerate further desensitizations with a less severe reaction or with no reaction. The greatest benefit of pretreatment with acetylsalicylic acid/montelukast was seen in patients with skin and respiratory symptoms, suggesting a dominant role for prostaglandins and leukotrienes in these manifestations of HSR to chemotherapy with platinum. Treating patients with only 1

dose of acetylsalicylic acid/montelukast 60 minutes prior to desensitization has made it possible to expand this treatment for use during desensitization with monoclonal antibodies. In addition, refractory skin and systemic reactions have been successfully blocked using this regimen.
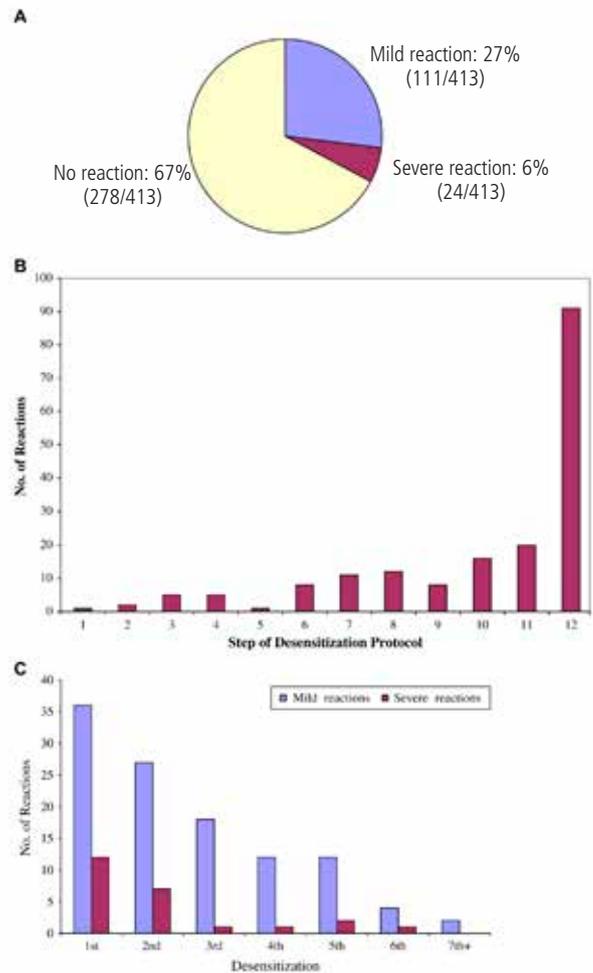

Figure 6. Outcomes and safety of desensitization for chemotherapy and monoclonal antibodies (adapted from Castells et al [21]).
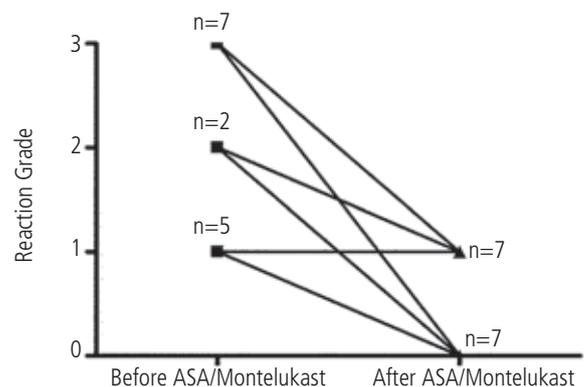

Figure 7. Evolution of severity of reactions during desensitization before and after pretreatment with acetylsalicylic acid/montelukast (adapted from Breslow et al [42]). ASA indicates acetylsalicylic acid.

Efficacy and Costs

There are no current studies of the costs of desensitization or the efficacy in terms of life expectancy of desensitized cancer patients. At the Brigham and Women's Hospital and Dana Farber Cancer Institute in Boston, we reviewed a population of 26 patients undergoing desensitization to carboplatin for recurrent cancer. Ten patients (38.5%) had a radiographic response (partial or complete) and/or >50% drop in their initial CA125 value, 11 (42.3%) had stable radiographic disease and/or a CA125 response (<50% drop), and 5 (19.2%) had progressive disease after completing their recommended carboplatin treatment. Of the 3 patients undergoing desensitization to paclitaxel for recurrent cancer, 1 had a clinical response to therapy, 1 had stable disease, and 1 had progressive disease (unpublished data). All of the 16 patients (100%) undergoing desensitization to paclitaxel for newly diagnosed cancer achieved clinical remission. Those are the expected rates for cancer patients not undergoing desensitization to chemotherapy, thus indicating that RDD protocols are effective. In addition, preliminary data suggest that costs are reduced for desensitized patients, since they are treated with first-line therapy with fewer complications and fewer visits to the emergency room (unpublished data).

Conclusions

RDD is both an acceptable approach in specialized patient care and a high-risk treatment modality, in which the risk is anaphylaxis and the benefit is increased quality of life and life expectancy. Successful desensitization requires categorization of the severity and nature of the initial HSR, skin testing, and risk stratification, leading to the establishment of an initial desensitization protocol, with adjustments based on the patient's response. Nurses and pharmacists play a critical role in the accurate and timely delivery of the protocol and in helping with the management of reacting patients. Breakthrough symptoms during desensitization are less severe than the initial HSR, and no deaths have been reported in the last 15 years. Reactions occurring days to weeks after drug treatment (eg, serum sickness, erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis) cannot be included in desensitization protocols at present owing to scant knowledge of their molecular targets and mechanisms.

Although the molecular basis of desensitization remains incompletely understood, mast cell models have provided evidence of profound inhibitory mechanisms of cell activation during desensitization, thus explaining the remarkable success of desensitization protocols when applied by trained allergists. These safety and efficacy outcomes provide grounds for the continued and expanded use of this approach for all patients for whom drug hypersensitivity would prevent the administration of first-line pharmacologic therapy. Desensitization should only be performed in settings with one-on-one (nurse-to-patient) care and where resuscitation personnel and resources are readily available. After a successful desensitization, repeated desensitization can be performed in outpatient or inpatient settings under similar conditions and with a variable patient:nurse ratio of 2:1. Education of nurses, pharmacists, oncologists, and allergy specialists will lead to the judicious use of desensitization protocols for patients with HSRs in need of first-line therapy. Basic research is needed to uncover the cellular and molecular mechanisms underlying the temporary tolerance induced by desensitization, so that pharmacological interventions can improve the safety and efficacy profile of this approach.

Conflicts of Interest

The author declares that she has no conflicts of interest.

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