Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases

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Background: Hypersensitivity reactions (HSRs) to chemotherapeutic drugs, including mAbs, often require that the provoking medication be discontinued, thus raising a dilemma for the caregiver: further use could precipitate a severe, even fatal, allergic reaction on re-exposure, but alternative drugs might be poorly tolerated or much less effective compared with the preferred agent.

Objective: We have developed a standardized rapid desensitization protocol for achieving temporary tolerization to drug allergens. In this study we evaluate the safety and efficacy of this protocol.

Methods: Ninety-eight patients who had HSRs in response to treatment with carboplatin, cisplatin, oxaliplatin, paclitaxel, liposomal doxorubicin, doxorubicin, or rituximab received rapid desensitization to these agents. A standardized 12-step protocol was used, with treatment given intravenously or intraperitoneally. Initial desensitizations occurred in the medical intensive care unit, whereas most subsequent infusions took place in an outpatient setting. Safety and efficacy of the protocol were assessed by review of treatment records.

Results: Of the 413 desensitizations performed, 94% induced mild or no reactions. No life-threatening HSRs or deaths occurred during the procedure, and all patients received their full target dose. Most reactions occurred during the first desensitization. Reactions were most commonly reported at the last step of the protocol. Desensitizations through the intravenous and intraperitoneal routes were equally effective.

Conclusions: Our standardized 12-step protocol for rapid drug desensitization is safe and effective and has been adopted as the standard of care at our institutions in treating patients with HSRs to chemotherapeutic drugs, including mAbs. (J Allergy Clin Immunol 2008;122:574-80.)

Key words: *Anaphylaxis, chemotherapy agents, monoclonal antibodies, rapid desensitization, hypersensitivity reactions, carboplatin, paclitaxel, adverse drug reactions*

Patients receiving multiple doses of chemotherapy can become sensitized to the drugs; subsequent exposure to these agents can lead to hypersensitivity reactions (HSRs)[1] and death.[2,3]

Patients treated with multiple courses of carboplatin have an increased rate of HSRs.[4] More than 27% of patients who receive more than 7 cycles of carboplatin have reactions, and half of those are moderate to severe.[1] Even on first exposure, approximately 16% to 40% of patients receiving paclitaxel infusions have HSRs, although the use of premedications has decreased this rate to less than 10%.[5] Interventions to limit HSRs with premedication, slowing infusion rates, or both are not always successful, however, and often permanent discontinuation of these medications is required.[6]

Temporary tolerization can be achieved in a relatively short period of time (typically 4-8 hours) with the use of rapid desensitization, a procedure that is designed and executed by a team consisting of allergists/immunologists, intensivists, and nurses. Through rapid desensitization, patients receive their target dose of medication in divided incremental steps. This methodology has emerged as a powerful tool for safely reintroducing medications that are beneficial for the management of patients with drug allergies. Despite the clinical expansion of rapid desensitization, its cellular and molecular mechanisms remain incompletely understood.[7]

We initially reported 77 desensitizations to paclitaxel and docetaxel and 35 desensitizations to carboplatin using a standardized 12-step protocol for inpatient use[8,9]; this was followed by 255 desensitizations targeted against multiple chemotherapeutic agents, including the mAb trastuzumab, which were administered in inpatient and outpatient settings.[10] We now present data, collected in 2005-2006, on the safety and efficacy of 413 drug desensitizations performed in 98 patients; we have used our protocol to administer carboplatin, cisplatin, oxaliplatin, paclitaxel, liposomal doxorubicin, doxorubicin, and rituximab. In addition, we

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Supported by the Ovations for the Cure Desensitization Program.

Disclosure of potential conflict of interest: D. E. Sloane has received honoraria from Genentech. F. I. Hsu has served as a coinvestigator for Dyax Corporation and has received a research grant from the American Academy of Allergy, Asthma & Immunology. N. A. Barrett has served as a coinvestigator for the National Institutes of Health and has served as a primary investigator for the American Academy of Allergy, Asthma & Immunology and Altana. D. I. Hong and T. M. Laidlaw have received training grant salary from the National Institutes of Health. S. N. Nallamshetty has received training grant salary from the National Institutes of Health and research grants from the American Academy of Allergy, Asthma & Immunology and GlaxoSmithKline. S. M. Campos has served as a research consultant for Genentech and has received research support from Genentech, Novartis, and Ortho-Biotechnology. The rest of the authors have declared that they have no conflict of interest.

Received for publication December 14, 2007; revised February 27, 2008; accepted for publication February 29, 2008.

Available online May 27, 2008.

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0091-6749/$34.00

doi:10.1016/j.jaci.2008.02.044

Abbreviations used
BWH: Brigham and Women's Hospital
DFCI: Dana Farber Cancer Institute
HSR: Hypersensitivity reaction
MICU: Medical intensive care unit

present the first report of intravenous desensitization to 2 chemotherapeutic agents performed in rapid succession (double desensitization) and of intraperitoneal desensitization to paclitaxel or cisplatin using the same protocol. The protocol was well tolerated and was uniformly successful, allowing for the continuation of critically important medications in patients with drug allergies.

METHODS

Patients

This collaboration between investigators at Dana Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH; Allergy and Medical Intensive Care divisions) was approved by the Human Research Committee (institutional review board protocol no. 2007-P-000050/1). Between January 1, 2005, and October 31, 2006, patients with known HSRs to chemotherapy were referred to the allergy service for rapid desensitization.

The inclusion criteria were (1) age greater than 18 years, (2) ability to provide informed consent, and (3) HSR to a chemotherapeutic drug or an mAb occurring during or shortly after (≤48 hours) the infusion. Patients with delayed reactions (>48 hours), serum sickness, Stevens-Johnson syndrome, or toxic epidermal necrolysis were excluded.

Initial reaction classification

Patients' initial HSRs were classified as mild (absence of chest pain, changes in blood pressure, dyspnea, oxygen desaturation, or throat tightness) or severe (including at least 1 of these). Symptoms and signs of HSRs were cutaneous (flushing, pruritus, urticaria, angioedema, and maculopapular rash), cardiovascular (chest pain, tachycardia, sense of impending doom, presyncope, syncope, hypertension, and hypotension), respiratory (sneezing, nasal congestion, dyspnea, coughing, wheezing, and oxygen desaturation), throat tightness, gastrointestinal (nausea, vomiting, diarrhea, abdominal pain, and bloating), and neurological/muscular (disorientation, hallucinations, vision disturbances, ringing/pounding in ears, unusual taste, back pain, and numbness/weakness).

Skin test for hypersensitivity

For skin prick testing, a drop of carboplatin (10 mg/mL), cisplatin (1 mg/mL), or oxaliplatin (5 mg/mL) was applied to the volar surface of the forearm. For intradermal injections, 0.03 mL of carboplatin (1 mg/mL and 10 mg/mL), cisplatin (0.1 mg/mL and 1 mg/mL), or oxaliplatin (0.5 mg/mL and 5 mg/mL) was injected.[9-11] These concentrations were based on our studies and the studies of others, one of which described negative intradermal skin test results to carboplatin in 836 of 898 tests.[4,12] Skin tests were performed at least 2 weeks after the initial HSR to minimize false-negative results; a positive reaction was defined as a wheal with a diameter of at least 3 mm larger than that produced by a negative control (diluent). Histamine (10 mg/mL) was used as a positive control.

Paclitaxel was not used for skin testing because its predictive value has not been demonstrated[8,13]; liposomal doxorubicin and doxorubicin were not used because of high cutaneous toxicity.[14]

Twelve-step rapid desensitization protocol

Diphenhydramine or hydroxyzine (25 mg administered orally or intravenously), famotidine (20 mg administered intravenously) or ranitidine (50 mg administered intravenously), and lorazepam (0.5-1 mg administered orally or intravenously as needed for anxiety) were administered 20 minutes before the initiation of the protocol. In addition, dexamethasone (20 mg administered orally) was administered the night before and the morning of paclitaxel desensitization, as dictated by oncology standards. β-Blockers were held for 24 hours before desensitization.

TABLE I. Desensitization protocol for rituximab IV (851 mg): Solution preparation

	Volume	Concentration	Total amount of drug in each solution (mg)
Solution 1	250 mL	0.034 mg/mL	8.510
Solution 2	250 mL	0.340 mg/mL	85.100
Solution 3	250 mL	3.377 mg/mL	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.

Three solutions (each 250 mL of water with 5% dextrose) were delivered in 12 consecutive steps at increasing infusion rates (Tables I and II). Solution 1 was a 100-fold dilution of the final target concentration (steps 1-4), solution 2 was a 10-fold dilution of the final target concentration (steps 5-8), and the concentration of solution 3 was calculated by subtracting the cumulative dose administered in steps 1-8 from the total target dose (steps 9-12); for paclitaxel, the volume of solution 3 was adjusted when the concentration of the solution was higher than the saturation point of the drug (<1.2 mg/mL). Steps 1 to 11 each took 15 minutes (the dose increased by 2- to 2.5-fold with each step), and step 12 was prolonged to complete the target dose. The total time of desensitization was 5.8 hours, but rarely, the infusion was abbreviated to 3.8 hours by using 100-mL solutions. Our success with this rapid protocol has not always been paralleled by the experience of other institutions.[15]

Initial desensitizations occurred in the medical intensive care unit (MICU), with one-to-one nursing. Subsequent desensitizations were carried out in a DFCI outpatient infusion center, although infrequently, 1 or more subsequent desensitizations were performed in the BWH MICU or on a BWH inpatient ward, always with one-to-one nursing. The interval between chemotherapy treatments was typically 3 to 4 weeks, as dictated by standard oncology protocols.

Two patients were desensitized to paclitaxel and carboplatin in rapid succession on the same day, with paclitaxel desensitization performed first, followed by carboplatin desensitization. Three patients were desensitized to paclitaxel or cisplatin through the intraperitoneal route.

Treatment of reactions during desensitization

Reactions during desensitization were treated by immediately pausing the infusion and administering diphenhydramine or hydroxyzine (25-50 mg administered intravenously). Oxygen and nebulized albuterol, famotidine (20 mg administered intravenously) or ranitidine (50 mg administered intravenously), and methylprednisolone sodium succinate (0.5 mg/kg administered intravenously) were administered for severe reactions. Epinephrine, 0.3 mL (1 mg/mL), was available at the bedside for use as needed. Once the reaction subsided, the protocol was restarted from the step at which it had been paused.

If patients experienced reactions and required repeat desensitizations with the same drug, we modified the protocol by prolonging the step before when the reaction occurred, adding an additional step, and/or administering prophylactic medication before the step at which the patient had a reaction.

RESULTS

Patient characteristics

Over 22 months, 98 patients with HSRs to chemotherapy, including rituximab, received rapid desensitization. Patients' ages ranged from 30 to 78 years (mean, 55 years). Ninety-seven patients were being treated for a malignancy (1 male and 96 female patients), and 1 patient was being treated for polymyositis. The most common malignancies were ovarian, breast, and

TABLE II. 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).

TABLE III. Patents' primary diagnoses and chemotherapeutic agents inducing HSRs

Diagnosis	No. treated	Primary/recurrent cancer	No. of HSRs by agent
Ovarian cancer	65	13/52	Carboplatin (48)
			Paclitaxel (16)
			Liposomal doxorubicin (2)
			Cisplatin (2)
Breast cancer	8	4/4	Carboplatin (3)
			Paclitaxel (4)
			Doxorubicin (1)
Peritoneal cancer	8	3/5	Carboplatin (5)
			Paclitaxel (2)
			Liposomal doxorubicin (1)
Endometrial cancer	5	3/2	Carboplatin (2)
			Paclitaxel (3)
Fallopian cancer	3	1/2	Carboplatin (2)
			Paclitaxel (1)
Lymphoma	2	0/2	Rituximab (2)
Sarcoma			
Endometrial sarcoma	1	0/1	Liposomal doxorubicin (1)
Leiomyosarcoma	1	0/1	Liposomal doxorubicin (1)
Uterine cancer	1	1/0	Paclitaxel (1)
Cervical cancer	1	0/1	Cisplatin (1)
Colon cancer	1	0/1	Oxaliplatin (1)
Other			
Epithelioid hemangioendothelioma	1	0/1	Paclitaxel (1)
Polymyositis	1	NA	Rituximab (1)
Total	98	25/72*	101†

*Total number of primary and recurrent cancers is 97. One patient presented with polymyositis.
†Total number of HSRs is 101. Three patients were treated with more than 1 drug.

peritoneal (Table III). Twenty-five patients were treated for primary cancers, and 72 were treated for recurrent cancers. Three patients had separate HSRs to 2 drugs, bringing the total number of HSRs to 101. Patients reacted to carboplatin (n = 60), paclitaxel (n = 28), liposomal doxorubicin (n = 5), doxorubicin (n = 1), rituximab (n = 3), cisplatin (n = 3), and oxaliplatin (n = 1). A history of atopy, including allergic rhinitis/conjunctivitis, asthma, food allergies, urticaria, eczema, and/or latex allergy, was elicited in 55 (56.1%) patients. Seventy-five (77%) patients had a history of atopy or prior adverse drug reactions (Table IV).

TABLE IV. Number of patients with a history of atopy, an adverse drug reaction, or both before presentation

		History of adverse drug reaction*	
		Negative	Positive
History of atopy†	Negative	23	20
	Positive	33	22

The total number of patients with a history of atopy, adverse drug reactions, or both is 75.
*History of any adverse drug reaction (as listed in the patient's medical record) before hypersensitivity reaction to current chemotherapy.
†History of atopy included allergic rhinitis/conjunctivitis, asthma, food allergies, urticaria, eczema, or latex allergy.

Characteristics of initial HSRs

In the 55 patients treated with carboplatin for whom treatment data were available, 40 (73%) experienced an HSR during the seventh to tenth exposure to the drug. Twenty-seven (96%) of 28 patients treated with paclitaxel experienced an HSR during the first exposure. Of the 5 patients receiving pegylated doxorubicin, 4 reacted during the first exposure and 1 reacted during the third infusion. The patient with an HSR to Adriamycin reacted on the second exposure. Three patients receiving rituximab reacted during the first, second, and fourth exposures.

The characteristics of initial HSRs experienced by patients are presented in Table V and Fig 1. Eighty-one patients experienced a severe reaction, and 20 patients presented with a mild reaction. The most common carboplatin-induced reactions were cutaneous, respiratory, gastrointestinal, and cardiovascular. Fifteen (25%) patients experienced throat tightness, and 2 patients had a sense of impending doom.

Paclitaxel-induced symptoms were cutaneous, cardiovascular, and neurological/muscular, with 10 (36%) patients experiencing back pain. Seven (25%) patients experienced throat tightness, whereas 1 patient had a sense of impending doom.

Three of 6 patients with HSRs to liposomal doxorubicin or doxorubicin had chest pain, and 2 had presyncope. Two of 3 rituximab-sensitive patients had severe pruritus, and 1 had a syncopal episode. All 3 cisplatin-reactive patients had flushing, 2 had a maculopapular rash, and 1 had a syncopal episode.

TABLE V. Symptoms and signs during initial HSRs in 98 patients

	Carboplatin (N = 60)	Paclitaxel (N = 28)	Liposomal doxorubicin/doxorubicin (n = 6)	Rituximab (n = 3)	Cisplatin (n = 3)	Oxaliplatin (n = 1)
Symptoms and signs, no. (%)						
Cutaneous	60 (100)	23 (82)	3 (50)	2 (67)	2 (67)	1 (100)
Flushing*	50 (83)	22 (77)	1 (17)	1 (33)	2 (67)	
Pruritus	42 (70)	3 (11)	2 (33)	2 (67)	1 (33)	
Urticaria/angioedema	16 (27)	3 (11)	1 (17)		1 (33)	
Maculopapular rash	13 (22)	3 (11)	1 (17)	1 (33)	2 (67)	1 (100)
Cardiovascular	34 (57)	21 (75)	4 (67)	2 (67)	2 (67)	1 (100)
Chest pain	13 (22)	14 (50)	3 (50)		1 (33)	
Tachycardia	6 (10)	4 (14)	1 (17)			1 (100)
Sense of impending doom	2 (3)	1 (4)				
Presyncope	12 (20)	9 (32)	2 (33)	1 (33)		
Syncope	3 (5)			1 (33)	1 (33)	
Hypertension	8 (13)	7 (25)				1 (100)
Hypotension	7 (12)	5 (18)	1 (17)	1 (33)	1 (33)	
Respiratory	24 (40)	12 (43)	1 (17)	1 (33)		1 (100)
Sneezing/nasal congestion	2 (3)	1 (4)				
Dyspnea	16 (27)	7 (25)	1 (17)	1 (33)		1 (100)
Coughing/wheezing	9 (15)	2 (7)				
Desaturation	4 (7)	7 (25)				
Throat tightness	15 (25)	7 (25)	1 (17)			
Gastrointestinal	25 (42)	12 (43)	1 (17)	1 (33)		
Nausea/vomiting/diarrhea	18 (30)	7 (25)	1 (17)	1 (33)		
Abdominal pain/bloating	14 (23)	7 (25)				
Neurological/muscular	9 (15)	11 (39)	2 (33)	1 (33)		
Disorientation	1 (2)					
Hallucinations	1 (2)					
Vision disturbances	2 (3)					
Ringing/pounding in ears	1 (2)		1 (17)			
Unusual taste	1 (2)		1 (4)			
Back pain		10 (36)	1 (17)	1 (33)		
Numbness/weakness	3 (5)	2 (7)		1 (33)		

*Defined as erythema, warmth, or both.

Oxaliplatin-induced dyspnea, palpitations, tachycardia, and hypertension occurred in 1 patient.

Skin test results

Sixty patients underwent skin tests to carboplatin, and 53 (88%) had positive results (Table VI). Fifty-nine of these patients were desensitized to carboplatin, and 1 was desensitized to cisplatin. Seven patients with carboplatin-negative skin test results were treated as follows: 1 patient, who had a delayed reaction at the site of the skin test (48 hours later), was desensitized; 2 patients' results converted to positive after several treatments and were desensitized after conversion; and 4 patients had a reaction after being treated without desensitization and, for their next treatments, were desensitized without repeat testing. Two cisplatin-reactive patients had positive skin test results and were desensitized. One patient with a negative skin test result to oxaliplatin was empirically desensitized because of the severity of the initial reaction.

Rapid desensitization experience

A total of 413 rapid desensitizations were performed with the 12-step protocol exemplified for rituximab in Tables I and II. The patient population consisted predominantly of women with ovarian cancer (Table III); 88.1% were desensitized to carboplatin (212 administered intravenously) and paclitaxel (140 administered intravenously and 12 administered intraperitoneally). Twenty-seven intravenous liposomal doxorubicin, 2 intravenous doxorubicin, and 7 intravenous rituximab desensitizations were carried out. For cisplatin, 5 desensitizations were intravenous, and 7 were intraperitoneal. One intravenous oxaliplatin desensitization was performed. Two patients underwent double desensitization to paclitaxel and carboplatin within the same day.

All patients were initially desensitized in the MICU. Subsequently, 83 desensitizations were performed on the inpatient ward, and 241 desensitizations were performed in the outpatient infusion center. All 413 desensitizations were performed with one-to-one nursing.

Reactions during desensitizations

Ninety-four percent of desensitizations elicited mild (111 [27%]) or no (278 [67%]) reactions, and 6% (24) elicited severe reactions (Fig 2, *A*), all of which were less severe than initial reactions. All reactions subsided when the infusion was paused and appropriate treatment was administered (see the Methods section). Epinephrine was used in only 1 case. No patient required transfer to a more acute care setting or intubation, and no deaths occurred. All patients received the full target dose.

A total of 180 reactions occurred, with some patients experiencing more than 1 reaction during a single procedure. Seven

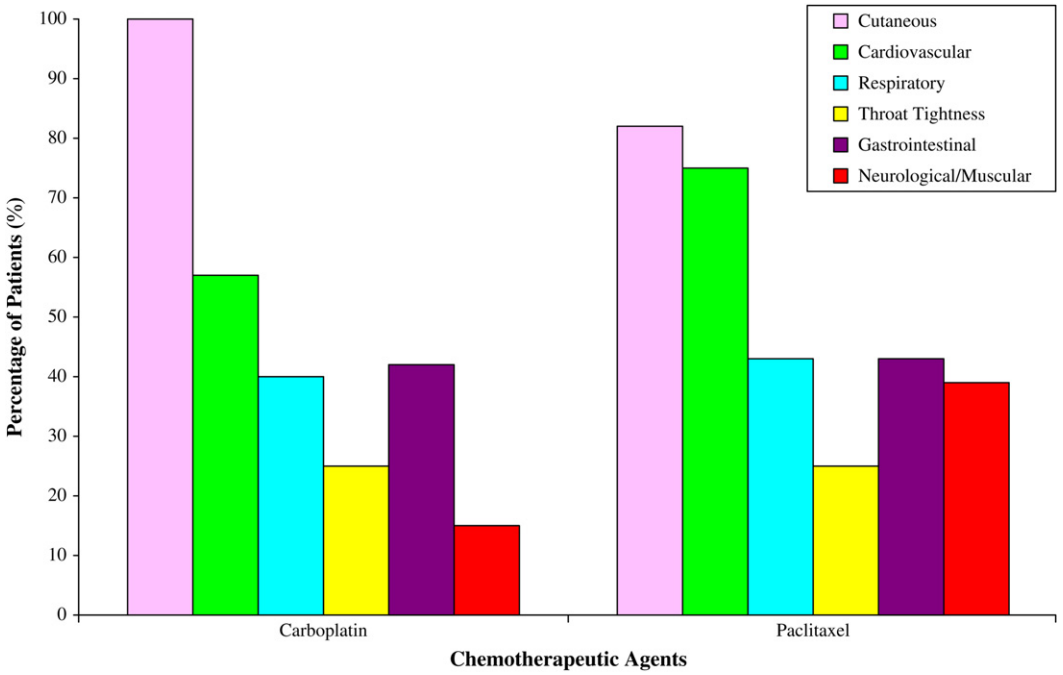

FIG 1. Frequency of symptoms and signs during initial HSRs.

TABLE VI. Carboplatin skin test results

	No. of patients (%)
Positive result	53 (88)
SPT, 10 mg/mL: 8	
ID, 1 mg/mL: 38	
ID, 10 mg/mL: 7	
Negative result	7 (12)
Total	60*

SPT, Skin prick test; *ID*, intradermal test.
*One patient with an HSR to cisplatin underwent skin testing with carboplatin.

percent of reactions occurred during the infusion of solution 1 (steps 1-4), 18% during infusion of solution 2 (steps 5-8), and 75% during infusion of solution 3 (steps 9-12; Fig 2, *B*). Ninety-one (51%) reactions occurred during the final step of the desensitization protocol.

For patients receiving multiple desensitizations (Fig 2, *C*), the majority of reactions occurred during the first 2 desensitizations (82 [61%]). Both the frequency and severity of reactions decreased with subsequent courses.

DISCUSSION

We present the results of the first large-scale series of desensitizations carried out in 98 patients by using the standardized protocol developed at our institutions. Over the course of 22 months, 413 rapid desensitizations to various chemotherapeutic agents, including rituximab, were performed, in which no deaths occurred; moreover, all patients received their full target dose, demonstrating the efficacy of the procedure. In our hands the protocol has been uniformly successful in permitting therapy for patients who are hypersensitive to chemotherapy drugs and mAbs.

Our study provides the first characterization of the symptoms of HSRs that are amenable to desensitization, demonstrates the uniform safety and efficacy of the protocol, including the first use of double desensitizations and intraperitoneal desensitizations, and suggests that carboplatin skin testing is a helpful predictor of reactivity.

We observed 2 patterns of initial HSRs that were amenable to desensitization. Patients sensitive to carboplatin typically presented on their seventh to tenth drug exposure with predominantly cutaneous, cardiovascular, respiratory, and gastrointestinal symptoms, a pattern consistent with anaphylaxis. These reactions are caused by the rapid release of preformed and newly synthesized mediators from sensitized mast cells through the cross-linking of FcεRI by drug antigens.[16] Patients reacting to paclitaxel, however, experienced chest pain, back pain, oxygen desaturation, hypertension, and presyncope on their first or second exposure, which are symptoms presumed to be due to IgE-independent mechanisms.[17] Nitric oxide synthesis, cytokine release, complement activation, and kinin production from direct mast cell activation, basophil activation, or both by polyoxyethylated castor in paclitaxel or by liposomes from doxorubicin are thought to be implicated in the pathogenesis of these HSRs.[18-20] Our data thus demonstrate that both IgE-mediated and non–IgE-mediated immediate HSRs of any severity are amenable to rapid desensitization.

Our experience suggests that after a successful initial desensitization in the MICU, it is safe to transition patients to the outpatient setting. Safety during rapid drug desensitization has been of paramount concern since the first description of desensitization to penicillin in pregnant women with syphilis.[21] Mechanisms of mast cell inhibition described *in vitro* have not been demonstrated *in vivo*, and the reintroduction of a drug antigen in a sensitized patient can induce fatal anaphylaxis.[2,3] The majority of rapid desensitizations in this study were uneventful; 24 severe reactions responded well to standard therapy and did not preclude completion of the protocol. In contrast to the popular belief that the initial steps of desensitization carry the greatest risk for the patient, the vast majority of reactions occurred during the infusion of the third solution, and most of these were seen

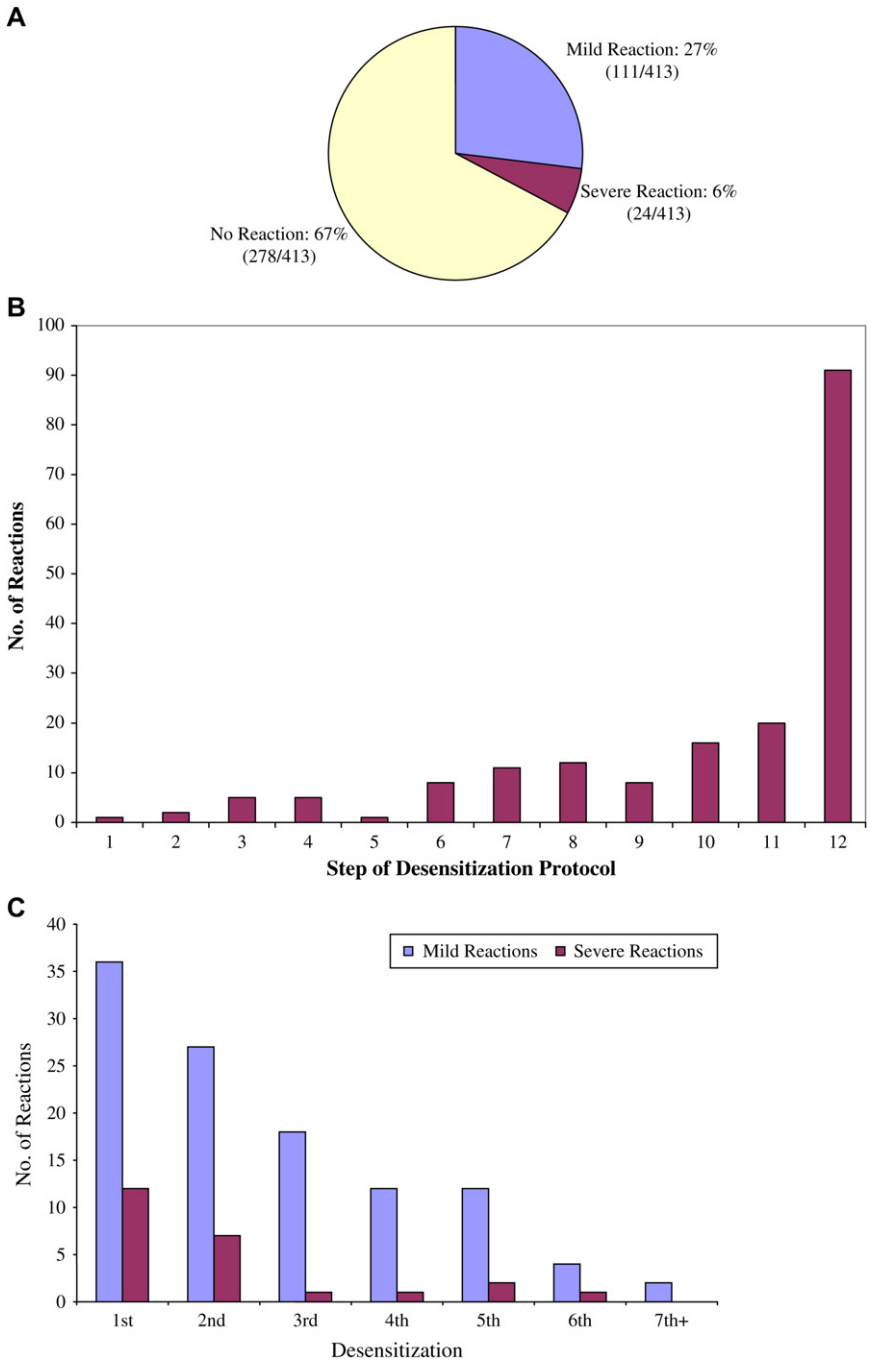

FIG 2. **A**, Number and severity of reactions during desensitization. A mild reaction was defined as absence of chest pain, changes in blood pressure, dyspnea, oxygen, desaturation, or throat tightness. A severe reaction included 1 of these. **B**, Desensitization step at which reactions occurred (total number of reactions = 180). **C**, Desensitization course at which reactions recurred (total number of reactions = 135 [111 mild and 24 severe]).

during the last step of the desensitization protocol. Over the course of multiple desensitizations, most reactions were seen in the first 2 desensitizations.

Two patients demonstrated hypersensitivity to 2 chemotherapeutic drugs and underwent double desensitization, with no increase in side effects. Intraperitoneal administration of paclitaxel and cisplatin has been shown to prolong survival in patients with stage III ovarian cancer.[22] Nineteen desensitizations through the intraperitoneal route were successful, with no acute or delayed side effects. Seven intravenous desensitizations involved rituximab, demonstrating that the protocol was effective for the administration of a class of medications that is structurally and biologically distinct from traditional anticancer agents. A 90-minute infusion of rituximab has been used in 150 patients with steroid premedication, and no adverse reactions were elicited.[23] Although decreasing the rate of infusion can minimize

rituximab-related reactions, a slower rate was not sufficient for eliminating HSRs to rituximab in our patient population, and only with desensitization were they able to tolerate treatment. It is possible that slowing the rate can address HSRs that are not immune mediated or IgE dependent.

Results of carboplatin skin testing were positive in 53 (88%) of 60 patients. Two patients with initially negative skin test results were given carboplatin treatments without desensitization but then converted to positive skin test results on subsequent testing. Four patients had a negative skin test result and had a mild reaction during the next carboplatin administration. We agree with others that a negative carboplatin skin test result puts the patient at low risk for anaphylaxis.[4] The uniformly negative paclitaxel skin test results support the hypothesis that reactions to this medication are IgE independent.[8]

Our study has a number of limitations. Our experience is highly biased toward female patients with certain types of cancer, and whether the success of our protocol can be generalized to treatment of male patients, to patients with other malignancies, and to patients hypersensitive to other medications remains to be determined. Nevertheless, we observed that the protocol was effective for drugs with different chemical structures and that presumably cause hypersensitivity through different mechanisms. Other publications, including a recent case report, corroborate the success of a similar protocol in another patient with an oxaliplatin-induced HSR.[24]

Future investigations need to define the cellular and molecular mechanisms underlying rapid desensitization. One possibility is that there is a threshold effect, such that HSRs during desensitization can be predicted when the cumulative dose reaches a critical value, as seen *in vitro* for mouse bone marrow mast cells exposed to suboptimal antigen.[7] Determining such a threshold for a given patient and drug would allow tailored modification of the protocol to circumvent reactions. Our study indicated that an allergic background is a risk factor for the development of HSRs to chemotherapeutic drugs: 76.5% of our patients had a history of allergy symptoms, twice that of the general population. Further studies are needed to confirm this association.

In conclusion, our standard protocol for rapid desensitization is safe and effective. Although it must be administered by an allergist/immunologist with specialty training and experience in drug desensitization, it is a powerful technique for overcoming hypersensitivity and thus represents an important means for continuing treatment with preferred therapeutic agents for our sickest patients.

We thank all of the nurses in the MICU at BWH and in the outpatient clinic at DFCI. We are indebted to all of our patients, and we appreciate their courage and willingness to undergo desensitization.

Clinical implications: Rapid intravenous and intraperitoneal desensitizations for HSRs to chemotherapy, including mAbs, are safe and effective. The 12-step protocol presented here is the standard of care at our institutions.

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