

Original Article

Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies

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What is already known about this topic? Rapid drug desensitization (RDD) is safe and effective.

What does this article add to our knowledge? The efficacy of a drug administered by RDD is maintained; patients treated with RDD do not incur greater costs than those treated by standard administration.

How does this study impact current management guidelines? Patients with hypersensitivity reactions to chemotherapeutics or monoclonal antibodies should be evaluated by an allergist and preferentially treated with first line therapy through RDD.

BACKGROUND: Rapid drug desensitization (RDD) is used to address hypersensitivity reactions to chemotherapeutics and monoclonal antibodies, allowing patients to be treated with optimal pharmacological agents. RDD protocols are tailored to each individual patient's reaction and needs, and protect against anaphylaxis, but overall risks, costs, and benefits have not been determined.

OBJECTIVE: We investigated the safety, efficacy, costs, and life expectancy of patients in a large population undergoing RDD.

METHODS: We analyzed 2177 RDD procedures performed in 370 patients with cancer, vasculitis, and hematological and connective tissue diseases who presented 402 reactions. A subgroup of carboplatin allergic patients with ovarian cancer treated with RDD was analyzed for costs and life expectancy and compared with a nonallergic control group.

RESULTS: RDD allowed all patients to receive safely the full dose of the medication to which they were reactive. A gradual increase in the fraction of outpatient desensitizations from 81% to 98% was achieved through risk stratification. Of the 2177 desensitizations, 93% had no or mild reactions whereas 7% had moderate to severe reactions, which did not preclude the completion of the treatment, and there were no deaths. Overall health costs in the carboplatin allergic group were not higher than those in the nonallergic group treated with standard of care. Administration of carboplatin through RDD was as effective as standard administration with a nonsignificant increase in life expectancy in desensitized patients as compared with nonallergic, nondesensitized controls.

CONCLUSIONS: RDD is cost effective and safe for allergic patients with cancer and chronic disease to remain on first line therapy. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: Drug desensitization; Chemotherapeutic agents; Monoclonal antibodies; Carboplatin; Drug hypersensitivity; Cost; Efficacy; Safety

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Traditional patient care dictates that when a patient has presented a hypersensitivity reaction (HSR) to a medication, strict avoidance is the soundest and safest option. For patients with malignancies, hematological diseases, and chronic inflammatory diseases, changing to a second line agent after an HSR may negatively impact quality of life and life expectancy. Rapid drug desensitization (RDD) is a procedure initially developed for antibiotic allergic patients with serious infections when no alternatives were available¹ such as the treatment of syphilis in

*Abbreviations used**HSR*-Hypersensitivity reaction*MoAbs*-Monoclonal antibodies*RDD*-Rapid drug desensitization

penicillin allergic pregnant women and recurrent *Pseudomonas* and *Klebsiella* infections in patients with cystic fibrosis.²⁻⁴ More recently, the application of RDD has been extended to address chemotherapy and monoclonal antibody (MoAb)-induced HSRs and anaphylaxis. We and others have provided initial evidence of the safety and efficacy of RDD⁵⁻⁸; however, legitimate concerns about RDD have been raised. RDD procedures have been performed in intensive care settings because of the intrinsic risk of inducing a severe HSR and anaphylaxis when re-exposing patients, and it has been hypothesized that the health care costs outweigh the benefits of the procedure. RDD protocols provide longer than the recommended infusion times, and peak drug concentrations may differ from standard administration with an unknown long-term impact on drug efficacy. Here we provide evidence that common chemotherapy drugs and MoAbs can be safely administered by a flexible standardized RDD protocol, provided the indications and risk assessment by expert allergists are enforced. We also provide evidence that the overall costs of desensitized patients are similar to nondesensitized patients, that drug efficacy is unaltered, and that there was a nonsignificant increase in life expectancy in carboplatin allergic patients when compared with nonallergic controls.

METHODS

Patients

The study was approved by the Partners Institutional Review Board (Brigham & Women's Hospital and Dana Farber Cancer Institute). Patients 18 years or older referred to the Drug Hypersensitivity and Desensitization Center between January 2007 and December 2010 with an HSR during or up to 48 hours after the infusion of chemotherapy or MoAbs was included. Patients with delayed reactions (>48 hours), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reactions with eosinophilia and systemic symptoms were excluded. Some patients reacted to and were desensitized to more than 1 drug. Six patients had initial reactions to cisplatin and were desensitized to carboplatin because they had positive skin tests to both cisplatin and carboplatin. Health care costs during the desensitization period and life expectancy of 171 patients with ovarian cancer and carboplatin allergy were compared with 181 nonallergic carboplatin-treated patients with ovarian cancer. The national death index provided data on deceased patients and cost data were obtained from the financial administration of Brigham and Women's Hospital. The components of the captured costs included noninfusion-related hospital visits (such as outpatient visits), emergency department visits, intensive care unit stays, surgical operations, and any associated nursing care and materials (such as medications, IV fluids, administration of transfusions, and other blood products). The direct costs of drug (chemotherapy or MoAb) administration (whether administered by regular infusion or by desensitization) were not available for this analysis. However, as the reported costs for both the desensitization group and the control group omit the direct expense of drug administration, the 2 groups are equivalent in this respect.

HSR symptoms, grading of severity, risk stratification, and skin testing

Immediate-type hypersensitivity manifestations included cutaneous, respiratory, cardiovascular, throat and tongue, gastrointestinal, neuromuscular, and general symptoms. Grade 1 reactions (mild) were limited to the skin, grade 2 (moderate) reactions met the criteria for anaphylaxis by involving 2 or more organ systems with or without skin involvement, and grade 3 (severe) anaphylactic reactions included 1 or more organ systems with vital sign changes such as hypo-/hypertension, oxygen desaturation, throat symptoms, or cardiovascular collapse.⁵ Skin testing was performed at least 2 weeks after the initial reaction to minimize false-negative results. Patients with grade 1 and 2 reactions were considered moderate risk⁵ and were desensitized in an outpatient infusion center. Patients with grade 3 reactions were considered high risk and were initially desensitized in the medical intensive care unit. As safety information on RDD increased, some patients with grade 3 reactions were desensitized in the outpatient unit. After successful intensive care unit desensitization, patients were desensitized in the outpatient setting.

Desensitization protocols and premedications

One to four solutions (each 250 to 300 mL of either water with 5% dextrose or saline) were delivered in consecutive steps at increasing infusion rates (see Ref. 5 for an example of a 12-step desensitization protocol and Figure 1 for a 16-step protocol). For paclitaxel, the volume of the final solution was adjusted to remain below the saturation point of the drug (1.2 mg/mL). Each step except the last took 15 minutes, and the doses delivered in a given step were 2 to 2.5 times that of the previous step. The last step was delivered at 80 mL/h to complete the target dose.

Premedications for desensitization (in addition to those, including corticosteroids, prescribed by the oncologist) were based on the patient's symptoms during the initial HSR. Antihistamines (H1 and H2 antagonists) were used prophylactically against pruritus, urticaria, or angioedema, whereas aspirin and montelukast were used to prevent flushing or bronchospasm. COX-1 inhibitors, steroids, and opioids were used for systemic symptoms including chills, rigors, fever, and pain. The treatment of reactions included pausing the infusion and administration of medications based on the symptoms. Once a reaction resolved, the protocol was resumed at the step at which it was paused and completed. On subsequent desensitizations, additional prophylactic premedications were added before the step at which the patient reacted. If the patient had breakthrough symptoms despite the additional prophylactic agents, an additional step was added before the reaction step and the dose recalculated to adjust for the additional step. Sixteen-step protocols were used for patients with initial grade 3 HSRs (Figure 1) and for patients with grade 3 reactions during a 12-step protocol. After 2 uneventful desensitizations, the final rate was increased to 120 and 160 mL/h at 15-minute intervals, and, on rare occasions, patients were desensitized with 1 or 2 bags after 2 successful increases of the final infusion rate. Intraperitoneal desensitizations were performed with the same protocols as IV, but preceded and followed by infusion of 500 mL of fluid intraperitoneally. Beta-blockers and angiotensin converting enzyme inhibitors were held for 24 hours before the desensitization.

Statistical analysis

The Pearson χ^2 and Fisher's exact tests were used for associations. The Cochran-Mantel-Hansel test was used to test for trends. For cost data analysis, we calculated descriptive statistics such as mean and standard deviation and used 2-sample, 2-sided *t*-tests to compare control and desensitized groups to each other. We also fit a nonlinear regression

Name of medication:		Gemcitabine					
Target Dose (mg)				1122.0			
Standard volume per bag (ml)				250			
Final rate of infusion (ml/hr)				80			
Calculated final concentration (mg/ml)				4.488			
Standard time of infusion (minutes)				187.5			
						Total mg per bag	
Solution 1	250	ml of	0.002	mg/ml	0.561		
Solution 2	250	ml of	0.045	mg/ml	11.220		
Solution 3	250	ml of	0.449	mg/ml	112.200		
Solution 4	250	ml of	4.453	mg/ml	1113.143		
				Volume infused per step (ml)		Cumulative dose (mg)	
Step	Solution	Rate (ml/hr)	Time (min)	Dose administered with this step (mg)			
1	1	2.5	15	0.625	0.001	0.001	
2	1	5	15	1.25	0.003	0.004	
3	1	10	15	2.5	0.006	0.010	
4	1	20	15	5	0.011	0.021	
5	2	2.5	15	0.625	0.028	0.049	
6	2	5	15	1.25	0.056	0.105	
7	2	10	15	2.5	0.112	0.217	
8	2	20	15	5	0.224	0.442	
9	3	5	15	1.25	0.561	1.003	
10	3	10	15	2.5	1.122	2.125	
11	3	20	15	5	2.244	4.369	
12	3	40	15	10	4.488	8.857	
13	4	10	15	2.5	11.131	19.988	
14	4	20	15	5	22.263	42.251	
15	4	40	15	10	44.526	86.777	
16	4	80	174.375	232.5	1035.223	1122.000	
Total time (minutes) =			399.375	= 6.66 hrs			

FIGURE 1. Desensitization protocol: example of a 4-bag, 16-step protocol. A patient presenting with a grade 3 anaphylactic reaction to gemcitabine was desensitized in the intensive care unit with 4 bags (250 mL) and 16 steps (15 minutes each step except for step 16). Four solutions were made as follows: solution 1 was a 1000-fold dilution of the final target concentration (steps 1-4), solution 2 was 100-fold dilution (steps 5-8), solution 3 was 10-fold dilution (steps 9-12), and solution 4 was calculated by subtracting the cumulative dose delivered in steps 1-12 from the total target dose (steps 13-16). The total time was 6.7 hours, and at the end of the desensitization protocol the full target dose was infused.

model to predict total costs by a number of encounters. To compare the survival rates of the 2 groups from date of first contact to date of death or last follow-up, we first used the nonparametric Kaplan-Meier estimator also known as the product limit estimator, with right censoring to summarize survival functions. Because patients who received desensitization differed from control patients, we compared survival using a propensity score analysis.^{9,10} Cohorts were balanced by weighted propensity scores obtained from a logistic regression model with age, stage, and year of service. For each patient, the weight was assigned as the inverse probability of belonging to the group that they are in (inverse probability of treatment weight). We then applied the weights to the Kaplan-Meier. All significance testing was performed at the 0.05 level. We used SAS Version 9.2 and R 3.1.1 for all analyses.

RESULTS

Patients, desensitizations, and skin testing

From 2007 to 2010, 370 patients (335 women and 35 men), 64% more than 65 years old, were evaluated for 402 HSRs to

chemotherapy and MoAbs, and received a total of 2177 desensitizations (Table I), of which 2155 had 12 to 16 steps and 22 had fewer than 12 steps (4 to 8 steps, Table IIB). The percentage of outpatient desensitizations increased from 2007 (81%) to 2010 (98%) with a corresponding decrease in intensive care unit cases (Table IIA). Atopy was present in 45% of the desensitized population, with rhinoconjunctivitis being the most common allergic condition (64%), followed by food allergies (20%) (Table IA). A history of other adverse drug reactions was present in 47% of the patients, but there was no significant association between atopy and history of allergic reactions to other medicines (Table IA) (Pearson χ^2 test: $P = .352$). Most of the initial chemotherapy reactions were induced by carboplatin (212 cases) and paclitaxel (86 cases), whereas most of the MoAbs reactions were induced by rituximab and infliximab (Table IC). The most common malignancies were ovarian and breast cancer with 78% (182 of 234) of the patients with ovarian cancer having recurrent disease and 67% (20 of 30) of the patients with breast cancer having primary disease (Table IB).

TABLE I. Patient characteristics

A. The sex and age distribution and associated atopic disease			
Patients		Total	
Age (mean ± SD)			
Female 57 ± 11	335 (91%)		
Male 56 ± 14	35 (10%)		
Age			
<25	6		
25-45	34		
45-65	94		
>65	236		
Atopy			
	Negative	202 (55%)	
	Positive	168 (45%)	
	Asthma	14	
	Rhinoconjunctivitis	107	
	Food allergy	35	
	Urticaria	12	
	History of other ADR	173 (47%)	
B. Diagnosis and drugs inducing the initial HSR			
Diagnosis	Patients	Primary/recurrent/NA	Drugs inducing initial hypersensitivity reactions (number)
Ovarian cancer	234	52/182	Carboplatin (180), paclitaxel (57), doxorubicin (9), cisplatin (4), docetaxel (4), IP paclitaxel (3), gemcitabine (1)
Breast cancer	30	20/10	Paclitaxel (11), docetaxel (5), trastuzumab (5), carboplatin (3), cisplatin (3), doxorubicin (2), cyclophosphamide (2)
Endometrial/uterine cancer/cervical cancer	20	8/12	Carboplatin (9), paclitaxel (9), cisplatin (2), doxorubicin (2)
Colon cancer	16	5/11	Oxaliplatin (15), cetuximab (1)
Lymphoma	11	2/9	Rituximab (10), methotrexate (1)
Peritoneal cancer	9	5/4	Carboplatin (7), paclitaxel (3), IP cisplatin (1), doxorubicin (1), bevacizumab (1), docetaxel (1)
Fallopian tube cancer	7	3/4	Carboplatin (6), paclitaxel (2)
Prostate cancer	6	3/3	Carboplatin (3), docetaxel (2), paclitaxel (1)
Lung cancer	4	2/2	Carboplatin (2), cisplatin (1), docetaxel (1)
Arthritis	9	NA	Infliximab (8), tocilizumab (1)
Anemia	3	NA	Rituximab (3)
CLL	3	NA	Rituximab (3)
Other: Waldenstrom’s macroglobulinemia (1), essential thrombocytosis (1), Wegener’s granulomatosis (1), Crohn’s disease (2), ulcerative colitis (2), polymyositis (1), systemic lupus erythematosus (1). Other cancers: bile duct (1), bladder (1), gastric (1), testicular (1), gonadoblastoma (1), throat (1), thyroid (1), tongue (1), vaginal (1)	18	NA	Rituximab (6), carboplatin (2), paclitaxel (3), infliximab (2), cisplatin (2), oxaliplatin (1), bevacizumab (1)
Total	370	5/4	402
C. Skin testing for each drug inducing an HSR			
Medication	Number of patients		Skin testing (% positive)
Carboplatin	212		194/197 (98%)
Paclitaxel intravenous	86		N/A
Paclitaxel intraperitoneal	3		N/A
Oxaliplatin	16		15/16 (93.8%)

(continued)

TABLE I. (Continued)

C. Skin testing for each drug inducing an HSR

Medication	Number of patients	Skin testing (% positive)
Doxorubicin	14	N/A
Cisplatin intravenous	12	10/11 (90%)
Cisplatin intraperitoneal	1	N/A
Docetaxel	13	N/A
Cyclophosphamide	2	2/2 (100%)
Methotrexate	1	1/1 (100%)
Rituximab	22	9/15 (60%)
Infliximab	10	4/9 (44.4%)
Trastuzumab	5	3/3 (100%)
Bevacizumab	2	2/2 (100%)
Tocilizumab	1	1/1 (100%)
Cetuximab	1	1/1 (100%)
Gemcitabine	1	N/A

ADR, Adverse drug reactions; CLL, chronic lymphocytic leukemia; HSR, hypersensitivity reaction.

A drop of the medication at a nonirritating concentration was placed on the volar surface of the arm along with a positive control (histamine 10 mg/mL) and a negative control (diluent). If no skin reaction was observed 15–20 minutes after percutaneous prick testing, intradermal injections (0.03 mL) at 1/100 and 1/10 of the percutaneous concentrations were performed. A wheal of at least 3 mm larger than the negative control with a flare was considered a positive reaction. Paclitaxel and docetaxel were not used for skin testing because the predictive value was unknown at that time. Skin testing to liposomal doxorubicin and gemcitabine was not performed because of the vesicant effect of these agents. Delayed skin test reactions were read at 24 hours.

TABLE IIA. Location of the initial and subsequent desensitizations per year from 2007 to 2010

	2007	2008	2009	2010	Total
HSRs	94	94	98	116	402
Patients	91	88	92	99	370
MICU	68 (19%)	72 (14%)	55 (10%)	13 (2%)	208
Outpatient	290 (81%)	438 (86%)	512 (90%)	729 (98%)	1969
Total	358	510	567	742	2177

HSR, Hypersensitivity reaction; MICU, medical intensive care unit.

Of 256 skin tests, 94% were positive at 15–20 minutes and 10 were delayed positive reactions within 24 hours (4%) (Table IC). Of 197 carboplatin skin tests, 194 (98%) were positive and 38 intradermal tests performed at the maximal concentration of 10 mg/mL, with 2 patients developing test site skin lesions that resolved with local steroid treatment. This 10 mg/mL dose is considered sufficient to elicit a response in patients with initial reactions over 6 months before testing.⁷ Sixty percent of the patients with HSRs to rituximab and 44% of the patients with HSRs to infliximab had positive skin testing (Table IC).

Breakthrough reactions during and after desensitizations

The majority of desensitizations had no (74%) or mild (19%) reactions (Figure 2, A), whereas moderate to severe reactions occurred in 154 desensitizations (7%). Paclitaxel desensitizations had the lowest rate of reactions (15%) as compared with carboplatin (32%) and rituximab (28%) (Figure 2, B). The majority of reactions during desensitization were cutaneous, followed by respiratory and gastrointestinal (Figure 2, C). During the time period analyzed, the percentage of patients with any breakthrough reaction decreased, and there was a corresponding increase in the percentage of patients who tolerated desensitization

TABLE IIB. Steps of the desensitization protocols used for RDD

Protocol steps <12	Number of desensitizations 22
12	2040
13	66
14	11
15	3
16	35
Total	2177

RDD, Rapid drug desensitization.

A total of 22 desensitizations were performed with fewer than 12 steps: 7 paclitaxel desensitizations with 5 steps, 5 carboplatin desensitizations with 8 steps, 3 carboplatin desensitizations with 4 steps, 3 bevacizumab desensitizations with 4 steps, and 4 rituximab desensitizations with 5 steps. Other: each representing less than 3 patients. Some patients had more than 1 HSR and were desensitized to more than 1 agent.

uneventfully (Table IIC). Some patients reacted more than once during a given desensitization and with multiple organ system symptoms, but no syncopal episodes occurred. Mild hypotension occurred during 4 carboplatin desensitizations, 1 oxaliplatin desensitization, and 1 paclitaxel desensitization. Intramuscular epinephrine was administered during 2 grade 3 reactions, 1 to carboplatin, and 1 to rituximab. In the first patient, the protocol was aborted, whereas in the second patient, the protocol was resumed and completed. Both patients were successfully desensitized with 16-step protocols. Regardless of the severity of the initial HSR, 58%–61% of patients had no breakthrough HSR on their first desensitization. For patients with initial grade 1 or 2 HSRs, the risk of a grade 3 breakthrough HSR was only 2%–3%, but was 9% for those with an initial grade 3 HSR (Table IID). The overall majority of breakthrough HSRs occurred during the last step of the protocol, but multiorgan system reactions were observed in highly reactive patients in early steps (bags 1 and 2). Reactions clustered on steps 7 to 12 for chemotherapeutics, and

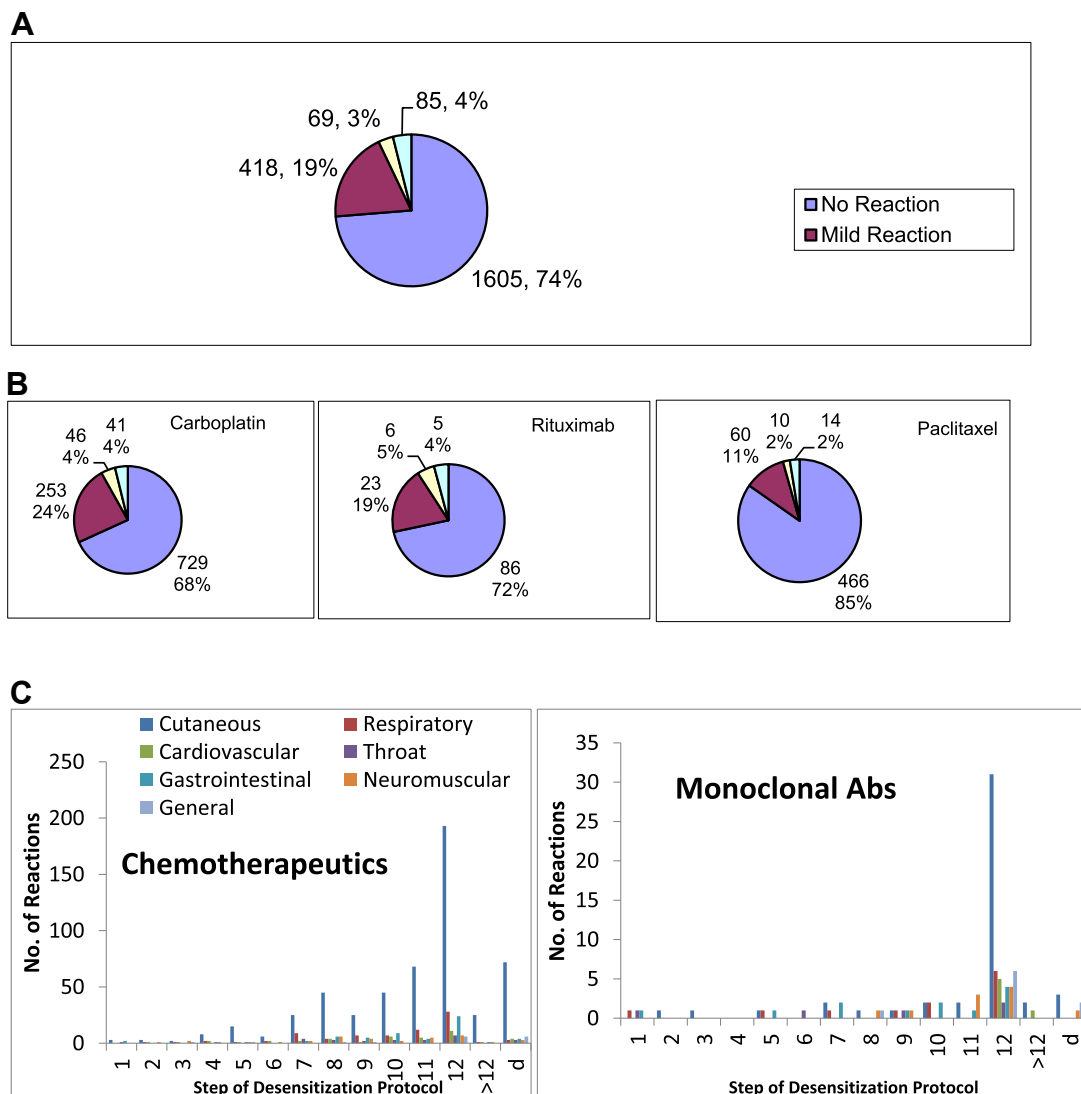


FIGURE 2. Safety of desensitizations. The overall number and severity of breakthrough reactions occurring during all desensitization courses is shown as a total of all desensitizations (2177) (A) and for carboplatin, rituximab, and paclitaxel, the most commonly desensitized drugs (B). Reactions at each step of the desensitization protocols are shown for chemotherapy and for monoclonal antibodies (C). Reactions after step 12 are indicated as >12 and delayed reactions as “d.”

TABLE IIC. Severity of the breakthrough reactions during the RDDs through consecutive years

Year	Desensitization reaction grade				Total
	0	1	2	3	
2007	236 (66%)	81 (23%)	18 (5%)	23 (6%)	358
2008	341 (67%)	126 (25%)	20 (4%)	23 (5%)	510
2009	434 (77%)	104 (18%)	15 (3%)	14 (2%)	567
2010	594 (80%)	107 (14%)	16 (2%)	25 (3%)	742
Total	1605	418	69	85	2177

RDD, Rapid drug desensitization.

Percentages represent the fraction of patients in a given year who experienced a desensitization breakthrough reaction (grade 0-3), and sum to 100% by rows.

TABLE IID. Comparison between breakthrough reaction severity during first RDD and initial HSR

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

HSR, Hypersensitivity reaction; RDD, rapid drug desensitization.

If there was no reaction during the first desensitization, a grade of 0 was scored. Percentages represent the fraction of patients with a given initial HSR (grade 1-3) who experienced either no reaction (grade 0) or a breakthrough reaction grade (1-3) during the first desensitization, and sum to 100% by rows.

A Costs for carboplatin -treated patients (primary and recurrent)

Patients and cost data	patients / encounters	age	total encounters	average (range) encounters/ patient	average cost*	total costs
Desensitized	171 / 146	62 (36-95)	532	3.1 (1 - 16)	\$6796	\$26,605
Control	186 / 170	57 (18-88)	592	3.2 (1 - 16)	\$9256	\$29,825

*significantly different between groups by t-test at $p < 0.0001$

B Plot of Kaplan-Meier survival curves from propensity-weighted data on carboplatin-treated recurrent cancer patients

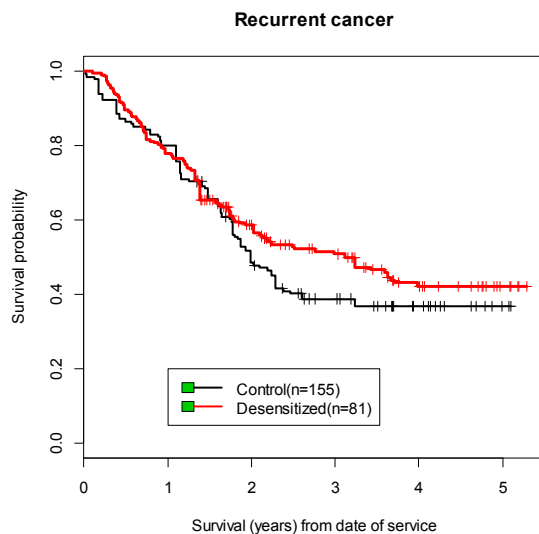


FIGURE 3. Survival and costs of desensitizations. Numbers of patients in each group are shown. Actual patient encounters involve patient returns to BWH outside of any standard oncology visits and DFCl. The average, compared by a 2-sample *t*-test, and total costs of these encounters are given during the time period 2007-2010. BWH, Brigham and Women's Hospital; DFCl, Dana Farber Cancer Institute.

on step 12 for MoAbs (Figure 2, C). Delayed reactions after desensitization occurred in 5% of the cases (112) and were mostly cutaneous, with fever occurring in oxaliplatin reactive patients.

Costs and life expectancy in carboplatin-desensitized patients

Carboplatin was the drug most frequently used in desensitizations and we used carboplatin-treated patients as a model to analyze the costs of desensitization and the life expectancy of desensitized patients. We looked at average hospital costs among 171 carboplatin-desensitized patients and 186 control carboplatin-treated but not desensitized patients during the period 2007-2010. Because control patients were not desensitized, the costs of desensitization were not included in the calculations. Average costs were calculated depending on hospital encounters, and control patients' costs were 31% higher than desensitized patients (Figure 3). Total costs per patient and number of encounters correlated for the desensitized ($r = 0.89$) and control groups ($r = 0.81$) separately using Spearman's correlation test ($P < .0001$). Using a nonlinear regression model, on average, a 1 unit increase in the number of encounters led to approximately \$7800 to \$8700 greater total costs for the desensitized and control group, respectively, and this was significant in both models ($P < .0001$).

Because the majority of patients with ovarian cancer referred for HSRs and desensitization had recurrent disease, we compared the life expectancy of 155 carboplatin-desensitized patients with recurrent ovarian cancers to 81 controls using propensity scores. Although there was a trend for increased life expectancy in the desensitized population, there were no significant differences between the 2 groups over a 5-year span after the year of service ($P > .05$) (Figure 3, B).

DISCUSSION

RDD is a multidisciplinary approach to drug hypersensitivity, allowing allergic patients to continue to receive their first line therapeutic agents while greatly minimizing the risk of anaphylaxis. Current recommendations for HSRs to chemotherapy call for increased premedication for grade 1 and 2 reactions and discontinuation for grade 3 reactions.¹¹ We and others have shown that RDDs are safe even for patients with grade 3 reactions, once patients are appropriately selected and risk stratified.^{5,6,12-15} In this study, we report 370 highly allergic patients (Table I) who received 2177 successful desensitizations to 15 drugs, 3 of which (bevacizumab, tocilizumab, and gemcitabine) are unprecedented. Importantly, there were no deaths associated with desensitization. This is the largest desensitization study worldwide, with the first cost analysis. Although the direct costs of desensitization were not analyzed, desensitized patients had less hospital encounters and overall costs than nondesensitized patients (Figure 3, A and B). This difference may be due to the relatively prolonged visit time (often more than 6 hours for desensitization vs 1-3 hours for standard infusions), as we have observed that desensitization patients were often able to receive IV fluids or meet with providers (NPs, MDs) while being desensitized, thus "bundling" services into a single visit that otherwise would require multiple separate appointments. Most importantly, carboplatin-desensitized patients had a nonstatistically significant lifespan advantage over nonallergic controls, indicating that the efficacy of carboplatin was not reduced in allergic patients and that RDD protocols are as effective as regular infusions (Figure 3, B). Interestingly, the frequency of atopy and other drug reactions was twice that of the general population (Table IA and see Lindelof et al¹⁶), but whether an allergy phenotype provides increased antitumor effects is currently undetermined.

Although IgE-mediated reactions were addressed by desensitization and the mechanisms underlying the inhibition of mast cell activation have been described *in vitro*,¹⁷ patients with negative skin testing, who had reactions atypical for classic mast cell activation and who therefore may have non-IgE-mediated reactions were also effectively treated with RDD (Table IC). These patients reacted mostly to MoAbs such as rituximab and infliximab, agents for which the negative predictive value of skin testing is unknown.

The safety of the flexible RDD multistep protocol is unprecedented, because patients presenting initially with anaphylaxis and desensitized in the intensive care setting proceeded to repeated successful desensitizations in the outpatient setting (Table IIA). Over the timespan of the study, a greater fraction of patients had no reaction (grade 0) during their first desensitization, and a lower percentage of patients had grade 3 reactions during the first desensitization (Table IIC), indicating that RDD became safer over time. Prognostically, patients with an initial

grade 1 or 2 HSR have a 91%-92% chance of having no (grade 0) or minimal (grade 1) symptoms during their first RDD. Patients with an initial grade 3 HSR have an 86% chance of having no or a minimal HSR during their first RDD, but continue to have a small chance (9%) of having a severe (grade 3) HSR on the first RDD (Table IID). Use of an extended 16-step protocol minimized breakthrough reactions, indicating that the initial steps were important.⁴ Although breakthrough reactions were most frequent during the last step (Figure 2, C), the threshold dose eliciting a reaction was unique to each patient, emphasizing the need for individualized protocols to provide protection against anaphylaxis. Although some chemotherapeutic agents and MoAbs have prolonged half-lives, delayed reactions were rare, indicating that desensitization provided prolonged protection (Figure 2, C). For patients with initial IgE-mediated anaphylactic reactions who present with severe reactions during desensitizations, preliminary clinical experience indicates that anti-IgE therapy may be protective, and ongoing studies are evaluating the utility of this agent as part of the approach to highly drug allergic patients.

RDDs should not be performed in patients when equally effective alternative therapies are available, because there is a nonzero risk of anaphylaxis, despite the remarkable safety of the multistep RDD protocol. Close collaboration among oncologists, allergists, nurses, and pharmacists is key to successful drug desensitizations. Given the profound protection against anaphylaxis and broad applicability demonstrated in this study, we propose the use of multistep RDD protocols for all medication allergic patients in need of first line therapies. Allergists have a unique role in evaluating patients with drug-induced HSRs and making recommendations for RDD.

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