

Outcome of 490 Desensitizations to Chemotherapy Drugs with a Rapid One-Solution Protocol



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What is already known about this topic? Rapid desensitization protocols are effective and safe and allow reintroduction of a drug in patients who are sensitized to it.

What does this article add to our knowledge? It shows our center experience with a new, shorter protocol using only 1 solution of the drug.

How does this study impact current management guidelines? It could contribute to abbreviated desensitization protocols, at least in selected patients, reducing cost and time and allowing desensitization to be available for more patients.

BACKGROUND: Hypersensitivity reactions to chemotherapy drugs are quite frequent. Desensitization for chemotherapy drugs has become an option to maintain first-line therapy in patients who have suffered such reactions.

OBJECTIVE: The objective of this study was to describe our experience in desensitization with antineoplastic agents using a rapid 1-solution protocol.

METHODS: We performed a 3-year prospective observational study recording all patients who were desensitized with this protocol. All patients signed an informed consent. Skin test was performed at concentrations previously described as nonirritant. Desensitization was performed using only 1 solution of the drug prepared following the manufacturer instructions. Most drugs were diluted in a volume of 500 mL. We started infusion at 5 mL/h and increased doses at 15-minute intervals to 10, 25, 50, 75, and 100 mL/h. If no reaction occurred, and if the pharmacokinetics of the drug allowed it, we stepped up to 150, 200, and 250 mL/h.

RESULTS: Ninety patients were desensitized to 93 drugs: oxaliplatin (30), carboplatin (16), paclitaxel (19), docetaxel (6), cetuximab (5), rituximab (6), and others (11). A total number of

490 procedures were performed. Sixteen patients (17.77%) presented 26 reactions (5.3%). Most reactions appeared in patients who were desensitized to platins and in patients with severe reactions. All but 3 cycles were completely administrated. No deaths or hospital admissions were recorded.

CONCLUSIONS: This 1-solution protocol for desensitization has demonstrated to be safe and useful in our study population, especially for mild-to-moderate reactions and nonplatinum drugs. If our results were reproducible in other centers and larger populations, they could contribute to simplifying protocols and making desensitization available for more patients. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1621-7)

Key words: Rapid drug desensitization; One-solution protocol; Drug allergy; Oxaliplatin; Carboplatin; Paclitaxel; Docetaxel; Cetuximab; Rituximab

Desensitization has proved to be safe and effective in management of hypersensitivity reactions to chemotherapy drugs. Different protocols have been described, most of them involving the use of 3 or more solutions of the drug.¹⁻³ Currently, the most popular approach is the rapid protocol of 3 solutions and 12 steps published before by Castells et al,² although faster 1- or 2-solution protocols have been recently described.⁴⁻⁶

The aim of this study was to present a prospective observational study showing our experience in desensitization with antineoplastic agents and monoclonal antibodies using a protocol with 1 solution of the drug.

MATERIAL AND METHODS

We recorded demographic and clinical data of patients who were desensitized to chemotherapy drugs or monoclonal antibodies for cancer therapy between January 2013 and December 2016. All patients were informed, and they signed an informed consent.

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Abbreviations usedCTCAE v.3- *Common Terminology Criteria for Adverse Events, Version 3.0*IDT- *Intradermal test*SPT- *Skin prick test*ST- *Skin test*

Severity of initial reaction was classified in 3 grades according to Brown's classification⁷ (Table I).

This study has been approved by our Institution's Ethical Committee (CI.PI-15/14).

Skin testing

Skin test (ST) was performed 1 or 2 weeks after the initial reaction in most patients.

Skin prick test (SPT) was performed on the volar surface of the forearm. Concentrations were 5 mg/mL for oxaliplatin, 1 mg/mL for cisplatin, 10 mg/mL for carboplatin, 6 mg/mL for paclitaxel, 1 mg/mL for docetaxel, 0.12 mg/mL for irinotecan, 2 mg/mL for cetuximab, 10 mg/mL for rituximab, and 10 mg/mL for leucovorin. Intradermal testing (IDT) was performed first at 1/1000 and, if negative, at 1/100 and 1/10 dilution of the concentration used for SPT.

Patients with immediate reaction to cetuximab underwent SPT with commercial extracts of cow and pork meat (Leti SA, Barcelona, Spain) to exclude sensitization to alfa-gal.⁸

Desensitization procedure

The decision to perform desensitization was made together with an oncologist and only on the basis of clinical indication. It was offered if the oncologist thought that a clinical benefit could be obtained from continuing the drug and the patient presented at least 1 reaction to a chemotherapy agent with type I hypersensitivity and/or moderate or severe infusion reaction compatible symptoms despite negative ST results.

Desensitization was not performed when symptoms were compatible with immune-mediated delayed reactions (hypersensitivity syndrome, Stevens-Johnson syndrome, serum sickness, or toxic epidermal necrolysis), when patient did not give his/her consent, or the oncologist did not advise continuation of the inciting drug.

Most procedures were performed in an outpatient setting, in the allergy unit or in the outpatient oncology unit. Hospitalization and/or stay in the intensive care anesthesiology unit were considered for patients with very severe reactions, previous concomitant diseases, and/or long chemotherapy protocols. All procedures were directly supervised by an allergist trained in desensitization.

All patients received dexchlorpheniramine 5 mg and ranitidine 50 mg intravenous 30 minutes before desensitization. Aspirin (200-500 mg every 24 hours since day before), montelukast (10 mg every 24 hours since day before), and cetirizine (10 mg every 12 hours since 3 days before) were given according to clinical symptoms and severity of the reaction.

Montelukast was given to all patients who had respiratory symptoms and to those patients with the previous history of asthma or chronic obstructive respiratory disease despite the type of reaction. Aspirin was given to all patients who did not have contraindication for it. We avoided it if there was recent surgery (in the 2 weeks before desensitization), thrombocytopenia, nonsteroidal anti-inflammatory drug hypersensitivity, active bleeding, or gastric ulcer. Most patients received 200 mg, some subjects with very severe

TABLE I. Brown's classification for grading generalized hypersensitivity reactions⁷

Grade	Symptoms
I Mild: skin symptoms	Generalized erythema, urticaria, periorbital edema, or angioedema
II Moderate: cardiovascular, respiratory, or gastrointestinal involvement	Dyspnea, stridor, wheeze, nausea, vomiting, presyncope, diaphoresis, chest or throat tightness, or abdominal pain
III Severe: hypoxia, hypotension, or neurologic compromise	Cyanosis or hypoxia ($SpO_2 < 92\%$), hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence

SpO_2 , Peripheral capillary oxygen saturation.

reaction or who reacted in a previous desensitization received 500 mg at the allergist discretion. Oral antihistamines were added in patients with severe reaction and/or highly positive ST, in patients who reacted in a previous desensitization, and in patients with previous chronic urticaria.

We also used corticosteroid (methyl prednisolone 1 mg/kg of weight or hydrocortisone 100 mg) in the first 15 patients and in patients desensitized to rituximab. Dexamethasone 20 mg was given orally 12 hours and 1 hour before the treatment to patients receiving paclitaxel, docetaxel, and pemetrexed.

In addition, premedication for antiemesis was prescribed by the oncologist according to the current guidelines.⁹ Drugs used included, not exclusively, metoclopramide, ondansetron, aprepitant, and palonosetron.

The desensitization protocol was performed, as we described previously,⁶ using 1 solution of the drug prepared following manufacturer instructions.

Briefly, the dose of each agent was calculated by the oncologist on the basis of the body surface area and clinical parameters. Drugs were prepared in sterile conditions by the Pharmacy Service to obtain a full-strength nondiluted solution that was used for desensitization. The total volume of the solution was 500 mL for platines, taxanes, and rituximab, 250 mL for cetuximab and calcium folinate, and 100 mL for pemetrexed. Concentration varied among patients and drugs, as it was the same concentration for a patient receiving the same dose in a standard infusion.

Infusion of the drug was initiated at 5 mL/h and increments were done each 15 minutes to 10, 25, 50, 75, and 100 mL/h. If no reaction appeared, and depending on the drug, 150, 200, and 250 mL/h were reached at 15-minute intervals.

When a reaction appeared, we stopped infusion and gave treatment if indicated. When symptoms resolved, we restarted the protocol in the last well-tolerated step.

Maximum rate of infusion never went beyond the recommended rate by the oncologist for each drug. Briefly, maximum infusion rates prescribed for any patient in our hospital are 250 mL/h for oxaliplatin, 500 mL/h for carboplatin, 250 mL/h for cisplatin, 175 mL/h for paclitaxel, 250 mL/h for docetaxel, 250 mL/h for calcium folinate, 250 mL/h for rituximab, and 250 mL/h for cetuximab. Table II shows an example of dosage for oxaliplatin.

RESULTS

Ninety patients (60 females, median age 57.34, standard deviation 10.02) underwent at least 1 desensitization procedure to

TABLE II. Example of dosing for 130 mg of oxaliplatin diluted in 525 cc of volume (0.247 mg/mL)

Rate (mL/h)	Time (min)	Accumulated time (min)	Volume (mL)	Accumulated volume (mL)	Dose (mg)	Accumulated dose (mg)
5	15	15	1.25	1.25	0.3	0.3
10	15	30	2.5	3.75	0.68	0.98
25	15	45	6.25	10	1.54	2.52
50	15	60	12.5	22.5	3.08	5.6
75	15	75	18.75	41.25	4.63	10.23
100	15	90	25	66.25	6.17	16.4
150	15	105	37.5	103.75	9.26	25.66
200	15	120	50	153.75	12.35	38.01
250	89.16	209.16	371.5	525	91.76	129.77

93 drugs. Table III displays data about severity of reactions and implicated drugs. Detailed demographic and clinical data of the 90 patients are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org. There were 33 mild, 49 moderate, and 11 severe reactions. Reactions to taxanes and monoclonal antibodies usually appeared in the first administration without previous exposition to the drug. Reactions to platinum agents occurred after at least 5 or 6 cycles if patients were in their first course of treatment or in the first or second cycle, when they had been treated with the same drug months or years before.

Platines ST results are displayed in Table IV. For the rest of drugs, ST were not systematically performed in all patients.

Only 2 patients underwent ST for paclitaxel, and 1 of them presented positive IDT. We also recorded a positive IDT in 1 of the 2 patients who reacted to calcium folinate. ST to docetaxel (N = 1), rituximab (N = 7), pemetrexed (N = 1), cetuximab (N = 2), and irinotecan (N = 2) were negative. SPT for mammal meats were all negative.

A total number of 490 procedures for 93 drugs were performed in 90 patients. Three patients received desensitization to 2 different drugs on different occasions.

Table E2 in this article's Online Repository at www.jaci-inpractice.org displays ST and desensitization results of all 90 patients.

We recorded 26 reactions in 16 patients. This means that in 82.22% of patients and 94.69% of treatments, no reaction appeared.

Eight of the 30 oxaliplatin patients (26.6%) presented 13 reactions in 154 cycles (8.44%). All 8 patients had positive ST. Four of these reactions were grade II and epinephrine was used in 2 cases. Two of these 4 patients decided to stop the procedure after the reaction.

In the carboplatin subgroup (N = 16), 4 patients (25%) presented 8 reactions in 67 cycles (11.94%). Three reactions were grade II, and 1 required epinephrine. All treatments were completely administered. Only 1 of these 4 patients presented carboplatin positive ST.

A grade I reaction occurred in all 3 cycles of 1 of the 3 cisplatin desensitized patients. Only 1 of 19 paclitaxel desensitized patients manifested a mild late reaction. One of 7 rituximab patients presented a moderate grade II reaction (hypertension, tachycardia, chills, and abdominal pain). Clinical symptoms were not clearly compatible with a type I hypersensitivity reaction, but we decided to stop the treatment. No reactions were recorded during desensitization to docetaxel, cetuximab, pemetrexed, doxorubicin, or irinotecan.

TABLE III. Distribution of drugs and severity of reactions

Drug	90 patients desensitized to 93 drugs			
	I	II	III	Total
Oxaliplatin	12	15	3	30
Carboplatin	8	6	2	16
Cisplatin	1	2	0	3
Paclitaxel	4	11	4	19
Docetaxel	0	6	0	6
Rituximab	3	3	0	6
Cetuximab	0	3	2	5
Irinotecan	2	0	0	2
Calcium folinate	2	0	0	2
Pemetrexed	0	1	0	1
Doxorubicin	1	2	0	3
n (%)	33 (35.48%)	49 (52.68%)	11 (11.82%)	93

No deaths, hospital admissions, or premedication-related adverse events were recorded. All but 3 treatments were completely administered. In 2 of them, the procedure was stopped at the patient's discretion.

Table V displays data about all the patients who presented a reaction. The identification number of each patient correlates with Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org.

Most patients who experienced reactions were desensitized to platinum agents and had more severe initial reactions and positive ST.

DISCUSSION

The 1-solution protocol described in this paper has shown a good tolerance and efficacy profile in our population, especially in patients desensitized to nonplatinum agents.

This is not the first 1-solution protocol described in the literature, but it is the largest series of cases in which this type of protocol has been applied. Some case reports and a 12-patient series have been previously published. In 2012, Hong et al¹⁰ described a 1-solution protocol, similar to ours, which was successfully used in a patient who was desensitized to cetuximab. More recently, Vidal et al⁴ published a series of 58 procedures in 12 patients who were desensitized with a new 1-solution protocol. Their study showed a safety and success rate similar to those with 3 or more solutions. In addition, our group has published a case report of desensitization to natalizumab using the protocol described here.⁶ Furthermore, on several previous

TABLE IV. Platines ST results

	Positive (%)		Negative (%)	Not assessable	Not performed	Total
Oxaliplatin	24 (80)	SPT: 2 IDT: 22	5 (16.66)	1 (severe dermographism)	0	30
Carboplatin	7 (43.75)	SPT: 0 IDT: 7	8 (50)	0	1	16
Cisplatin	3 (100)	SPT: 0 IDT: 3	0	0	0	3
Total	34 (69.38)	SPT: 2 IDT: 32	13 (26.53)	1	1	49

IDT, Intradermal test; ST, skin test; SPT, skin prick test.

reports, most reactions occurred with the third and more concentrated solution.^{2,3,5,10,11} It is more evident for taxanes and monoclonal antibodies.^{5,8,10,11} This has led to some authors to propose simplified 2-solution protocols for selected patients on the basis of the severity of the initial reaction, ST results, and comorbidity.⁵

Our study has some limitations. Most of them are due to logistic and organization features and clinical practice variability.

First of all, ST were not systematically performed in all patients. We did not perform them in most patients who reacted to taxanes because in previous studies ST were reported to be of low usefulness.^{2,12} Most patients who react to taxanes do it in their first or second administration, and it was thought that it ruled out an IgE-mediated mechanism. However, in more recent studies, positive ST to taxanes have been found, and skin testing has been proposed for risk stratification. The authors suggest that these subjects could be previously sensitized to yew (*Taxus baccata*) and cross-react to taxanes in their first administration.⁵ Yew is not present in our media (Canary Islands) although we cannot exclude its role in patients who had lived before in other areas. In fact, we found 1 positive IDT to paclitaxel in a patient who was evaluated in 2013. Unfortunately, we have no information about where he had lived previously.

Other patients did not undergo ST because they were on steroid and/or antihistamine treatment that could not be stopped, or we were not able to perform them before the next cycle date for nonclinical reasons.

Carboplatin ST were not as reliable as they were in other previous reports. This is probably due to the short interval between the reaction and ST—1 or 2 weeks in most patients. An interval of at least 6 weeks is recommended to increase the sensitivity of ST.¹³ Nonetheless, we performed studies as soon as possible to administer the next cycle on the planned date. This decision was made together with the oncologist. We were aware that it would reduce ST sensitivity, but desensitization was programmed despite ST results, so we preferred to maintain continuity of the treatment.

We did not perform drug challenges either. Controlled challenge is the gold standard in drug allergy diagnosis, and some authors recommend it for chemotherapy agents.¹⁴ We decided to desensitize all patients who had an indication for the drug with no preliminary challenge. This could have led to a number of “false allergic patients” into the study population, but we preferred to avoid new reactions as much as possible. Most patients were worried about the risk of new reactions, and we thought some of them would be reluctant to undergo desensitization after a positive drug challenge. Thus, we decided

together with the oncologist to give priority to patient safety over allergological study.

Finally, there was some variability on the premedication used for desensitization or the decision about performing desensitization or changing treatment.

Premedication was prescribed by the allergist for each patient based on the severity of the initial reaction, type of symptoms, comorbidity, and ST results. For the first patients, we used only corticosteroids and antihistamines. Twelve patients were desensitized only with corticosteroid and antihistamines and 6 of them presented reactions, so we added aspirin and/or montelukast. The new premedication regime improved tolerance to desensitization. Currently, we rarely use corticosteroid, except for taxanes and rituximab.

There is sufficient evidence regarding the usefulness of aspirin and montelukast in preventing reactions during desensitization.¹⁵ Aspirin doses vary among series. We used 200 mg for most patients and 500 mg in patients who reacted with 200 mg and/or presented with a very severe initial reaction or highly positive ST, if they had no other contraindication for aspirin use. The main risk with aspirin is bleeding. This risk is greater in patients with thrombocytopenia or who are receiving treatment with the anti-vascular endothelial growth factor bevacizumab.

The decision to perform desensitization or change the treatment was subjected to bias too. It was decided on the basis of the oncologist's clinical criteria and patient's desires, so it is probable that patients with very severe reactions were more likely to be switched to another treatment or were not even referred for evaluation. In fact, the percentage of patients with Brown's grade III initial reactions was low in our population (11.8%) compared with other series. Brennan et al's¹¹ series of desensitization to monoclonal antibodies used Brown's classification and reported 26% of grade III reactions. In other studies,^{2,4} reactions were classified in 2 grades (mild or severe) depending on the presence or absence of some features (dyspnea, throat tightness, changes in blood pressure, chest pain, and oxygen desaturation). If we applied this classification to our population, we would have 46 (50%) severe reactions. Castells et al's (2008) study² and Vidal et al's (2017) study⁴ reported 80% and 75% rate of initial severe reactions, respectively.

We had an overall 5.3% rate of reactions during desensitization. This is lower than the results described by Castells et al² (33%) and Brennan et al¹¹ (29%), probably because they included more patients with severe reactions in their studies.

Madrigal-Burgaleta et al's (2013) study³ population and results may be more comparable with ours. They used National

TABLE V. Description of reactions

ID	Drug	ST	Severity of initial reaction	Premedication	No. and severity of reactions	No. of cycles	Management and outcome
2	Cisplatin	+ (IDT)	II	CCT, D	3 I (rash) in all 3 cycles	3	All treatments completed. Stopped because of progression Required antihistamine and steroid
5	Oxaliplatin	+ (IDT)	II	CCT, D	1 II in cycle 5. Rash and bronchospasm	5	Cycle 5 was not completed. Stopped because of reaction. Resolved with salbutamol, antihistamine, and steroid treatment
6	Carboplatin	—	I	ASA 200, M, R, D	1 I in cycle 6. Rash	6	Resolved with antihistamine All treatments completed. Stopped because of progression
9	Carboplatin	+ (IDT)	II	CCT, D	2 I in cycle 2 and II (rash and abdominal pain) in cycle 3	3	All treatments completed. Stopped because of progression and reactions Resolved with antihistamine, steroid, and ranitidine
10	Oxaliplatin	+ (STP)	II	CCT, D.	2 I in cycles 1 and 2. Rash	10	Resolved with antihistamine and steroid All treatments completed. ASA 500 mg, M and R were added since cycle 3 with no reaction in following 8 cycles
13	Oxaliplatin	+ (IDT)	I	CCT, D	1 I in cycle 1. Rash	1	Resolved with antihistamine Treatment completed. Stopped because of progression and reaction
14	Oxaliplatin	+ (IDT)	II	CCT, D, ASA 200, M, R	1 I in cycle 2. Mild rash in face 24 h after administration	2	Reaction resolved with cetirizine. Stopped because of neuropathy
28	Paclitaxel	NP	III	ASA 200, M, R, D	1 I en cycle 1. Rash in arms 6 h later	14	Reaction resolved with no treatment. No reaction in 13 following cycles. Stopped because of progression
30	Oxaliplatin	+ (IDT)	III	ASA 200, M, R, D	1 II (rash, abdominal pain, and dyspnea) in cycle 1	1	Required epinephrine, antihistamine, and steroid to resolve. Patient decided to stop the procedure. Treatment was not completed
32	Oxaliplatin	+ (IDT)	I	ASA 200, M, R, D	3 II (rash, palm itching, and dysphonia) in cycle 1. Palm itching in cycles 2 and 3	4	Reaction in cycle 1 required epinephrine. Added ASA 500 and cetirizine in cycles 2 and 4. Completed all cycles. Stopped because of progression
38	Oxaliplatin	+ (IDT)	II	ASA 200, M, R, D	2 II in cycle 1 (rash and abdominal pain), I in cycle 2 (rash)	4	Reaction in cycle 1 was managed with antihistamine, steroid, and ranitidine Added ASA 500 and cetirizine since cycle 2. No reaction in cycles 3 and 4. Completed all cycles and ended planned treatment
40	Carboplatin	—	III	ASA 200, M, R, D	1 I in cycle 1 (rash)	6	Treatment was completed. No reaction in the 5 following cycles.

(continued)

TABLE V. (Continued)

ID	Drug	ST	Severity of initial reaction	Premedication	No. and severity of reactions	No. of cycles	Management and outcome
42	Carboplatin	– (2 times)	II	ASA 200, M, R, D	4 II (bronchospasm in cycles 4 and 5), I (rash) in cycles 6 and 7	8	Reaction in cycle 4 required epinephrine. STs were repeated after first reaction and remained negative. ASA 500 added in cycle 8 with no reaction. All treatments were completed. Stopped because of progression
43	Calcium folinate	+ (IDT)	I	ASA 200, M, R, D	1 I (rash) in cycle 1	3	All cycles were completed and ended planned treatment
47	Rituximab	–	II	R, D, paracetamol	1 II unclear mechanism (hypertension, tachycardia, chills)	1	Treated with steroid and paracetamol. Treatment was not completed. Stopped because of reaction
69	Oxaliplatin	+	II	M, D, R	1 I (rash in cycle 2)	5	All cycles were completed. ASA 200 was added since cycle 3 with no reaction in cycles 3 and 5. Stopped because of progression

ASA, Acetyl salicylic acid; CCT, corticosteroids; D, dexchlorpheniramine; IDT, intradermal test; M, montelukast; R, ranitidine; SPT, skin prick test; ST, skin test.

Cancer Institute classification Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE v.3)¹⁶ and reported 65% of initial moderate-to-severe (grade II-IV) reactions and breakthrough reactions in 6% of cycles. Of course, both classifications are different, but most clinical features of CTCAE 2-4 and Brown's grades II-III overlap, and we have 64.5% of grade II-III initial reactions.

Most reactions in our series were related to platinum drugs, and especially to oxaliplatin in patients with positive ST. If we considered only patients with severe reactions to platins (N = 5), a reaction appeared in 40% of patients and 9.1% of cycles.

Patients with severe grade III reactions represented only a small fraction of our study population, so we cannot extrapolate results to this group of patients until larger studies, including more patients with severe reactions, have been performed. Currently, risk stratification is always mandatory before including a patient in an abbreviated protocol.

On the other hand, for mild and moderate reactions, and especially for nonplatinum drugs, this protocol seems to be comparable with those described with 3 or more solutions of the drug and it is simpler and less time consuming. In addition, stability of the drug would be assured by using only 1 undiluted solution.⁴ More studies including a larger number of patients are necessary to optimize the protocol and determine if these results are reproducible in other populations and in patients with more severe reactions.

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TABLE E1. Clinical and demographical characteristics of the patients and description of initial reactions

ID	Age (y)	Sex	Type of cancer and stage	Drug	Symptoms of initial reaction	Brown's grade	Infusion number in which reaction appeared
1	66	M	Colon IV	Oxaliplatin	Rash	I	13
2	56	F	Ovary IV	Cisplatin	Urticaria, itching, bronchospasm	II	1 (previously exposed to carboplatin 12 times)
3	47	M	Colon IIIC	Oxaliplatin	Rash, dyspnea	II	2
4	49	F	Breast IV	Docetaxel	Rash, dyspnea	II	2
5	44	M	Colon IV	Oxaliplatin	Dysphagia, dysphonia, bronchospasm, palm and plant itching, rash	II	6
6	58	F	Ovary IIIC	Paclitaxel	Bronchospasm	II	1
6	Second reaction			Carboplatin	Rash	I	9
7	66	M	Colon IV	Oxaliplatin	Rash, palm and plant itching	I	8
8	35	M	Hemangioendothelioma	Paclitaxel	Severe bronchospasm, SpO ₂ 78%	III	2
9	55	F	Ovary IV	Carboplatin	Chest tightness, itching, rash	II	8
10	51	F	Colon IV	Oxaliplatin	Palm and palm itching, rash, vomiting, abdominal pain	II	9
11	57	F	Ovary IIIC	Carboplatin	Dyspnea, palm itching	II	20
12	48	F	Lung IV	Carboplatin	Severe bronchospasm, blood pressure 88/50, rash, vomiting	III	7
13	65	F	Rectum IV	Oxaliplatin	Rash	I	15
14	63	M	Pancreas	Oxaliplatin	Rash and abdominal pain	II	10
15	48	F	Rectum IV	Oxaliplatin	Urticaria, palm itching	I	6
16	58	F	Breast IV	Docetaxel	Bronchospasm, rash	II	1
17	70	F	Ovary IIIC	Carboplatin	Rash, dyspnea, palm itching	II	13
18	47	F	Colon IV	Cetuximab	Rash, moderate bronchospasm	II	15
19	66	M	Colon IV	Oxaliplatin	Severe bronchospasm, syncope	III	9
20	61	F	Ovary IIIC	Paclitaxel	Rash, chest pain	II	1
21	43	F	Breast T2N2a	Docetaxel	Rash, chest tightness	II	3
22	59	F	Duodenum IV	Oxaliplatin	Rash and digestive symptoms	II	8
23	48	F	Ovary IV	Paclitaxel	Rash and dyspnea	II	1
23	Second reaction			Doxorubicin	Rash	I	2
24	44	F	Colon IV	Cetuximab	Rash, moderate bronchospasm	II	2
25	62	M	Colon IV	Oxaliplatin	Rash	I	7
26	59	M	Colon IV	Oxaliplatin	Rash, abdominal pain, bronchospasm	II	6
26	Second reaction			Cetuximab	Cyanosis, dyspnea, hypotension	III	1
27	58	M	Colon IV	Oxaliplatin	Rash and palm itching	I	11
28	62	F	Lung T2 N2 M0	Paclitaxel	Severe bronchospasm, SpO ₂ 76%, vomiting, abdominal pain	III	1
29	70	M	Colon IV	Oxaliplatin	Rash, angioedema	II	16
30	56	M	Colon IV	Oxaliplatin	Rash, dysphagia, incontinence	III	7
31	61	F	Ovary + Colon IV	Carboplatin	Rash, dyspnea	II	11
32	61	F	Colon IV	Oxaliplatin	Palm itching, rash	I	12
33	46	F	Breast T2 N1 M0	Paclitaxel	Rash, bronchospasm	II	1
34	74	F	Cervix IV	Paclitaxel	Bronchospasm, cyanosis, rash, SpO ₂ 89%	III	2
35	40	F	Cervix IV	Paclitaxel	Rash	I	1
36	64	M	Colon IV	Oxaliplatin	Rash, chest pain	II	6
37	37	M	Colon IV	Oxaliplatin	Rash, angioedema, chest pain	II	11
38	32	F	Colon IV	Oxaliplatin	Urticaria	II	7

(continued)

TABLE E1. (Continued)

ID	Age (y)	Sex	Type of cancer and stage	Drug	Symptoms of initial reaction	Brown's grade	Infusion number in which reaction appeared
39	72	M	Colon IV	Oxaliplatin	Hypotension, incontinence, syncope	III	>15
40	59	F	Ovary IV	Carboplatin	Blood pressure 82/60, urticaria, dysphagia, dysphonia	III	13
41	68	F	Breast	Paclitaxel	Rash and bronchospasm	II	1
42	56	F	Mesothelioma	Carboplatin	Bronchospasm, rash	II	6
43	72	F	Colon IV	Calcium folinate	Rash	I	13
44	55	F	Breast	Docetaxel	Bronchospasm, hypertension	II	2
45	62	F	Colon III	Oxaliplatin	Dysphagia and palm itching	II	4
46	79	F	Non-Hodgkin's lymphoma	Rituximab	Hypertension, low back pain	I	2
47	60	M	Non-Hodgkin's lymphoma	Rituximab	Hypertension, tachycardia, obnubilation	II/Unclear mechanism	8
48	60	F	Ovary IIIC	Carboplatin	Rash and palm itching	I	9
49	55	M	Kaposi sarcoma	Doxorubicin	Rash and bronchospasm	II	1
50	65	M	Colon IV	Oxaliplatin	Rash	I	13
51	58	M	Colon IV	Irinotecan	Rash, angioedema	I	14
52	50	M	Cavum	Cetuximab	Severe bronchospasm, SpO ₂ 44%	III	1
53	42	F	Breast	Paclitaxel	Rash and gastrointestinal	II	8
54	71	F	Ovary IV	Carboplatin	Rash and itching	I	8
55	71	M	Mesothelioma IV	Pemetrexed	Bronchospasm, dysphonia	II	1
56	65	M	Colon IV	Oxaliplatin	Rash and palm itching	I	20
57	42	F	Colon III	Oxaliplatin	Rash, dysphagia	II	7
58	53	M	Non-Hodgkin's lymphoma	Rituximab	Rash	I	1
59	45	F	Ovary IIIC	Paclitaxel	Rash and abdominal pain	II	1
60	51	F	Colon	Cisplatin	Rash	I	6
61	47	F	Breast	Docetaxel	Rash, gastrointestinal symptoms	II	1
62	55	F	Breast IV	Paclitaxel	Rash	I	1
63	56	F	Ovary	Carboplatin	Palm itching	I	8
64	45	F	Breast IV	Carboplatin	Palm itching, abdominal pain	II	11
65	52	M	Colon	Oxaliplatin	Palm itching, rash	I	8
66	47	M	Non-Hodgkin's lymphoma	Rituximab	Rash	I	1
67	62	F	Non-Hodgkin's lymphoma	Rituximab	Rash, abdominal pain	II	1
68	51	F	Cervix	Cisplatin	Rash, dyspnea	II	6
69	76	M	Colon	Oxaliplatin	Bronchospasm	II	16
70	73	F	Ovary	Carboplatin	Rash	I	7
71	72	F	Non-Hodgkin's lymphoma	Rituximab	Chills, tachycardia	II/Unclear mechanism	1
72	70	F	Ovary	Paclitaxel	Severe bronchospasm, SpO ₂ 65%	III	1
73	57	F	Ovary	Paclitaxel	Flushing, back pain	II	1
74	60	M	Lung	Carboplatin	Rash	I	9
75	63	F	Colon IV	Oxaliplatin	Rash and mild bronchospasm	II	14
76	61	F	Endometrium	Carboplatin	Rash and palm itching	I	10
77	65	M	Colon III	Oxaliplatin	Rash	I	7
78	52	F	Cervix	Carboplatin	Rash	I	5
79	65	F	Colon III	Oxaliplatin	Rash and palm itching	I	9
80	55	F	Lung	Docetaxel	Mild bronchospasm	II	9
81	50	M	Colon	Oxaliplatin	Rash and dyspnea	II	7
82	43	F	Breast	Paclitaxel	Dyspnea and abdominal pain	II	1
83	66	F	Breast IV	Paclitaxel	Rash	I	1
84	70	F	Colon	Calcium folinate	Urticaria	I	14
85	59	M	Lung	Paclitaxel	Rash and abdominal pain	II	3
86	44	F	Lung IV	Paclitaxel	Rash and tachycardia	I	1

(continued)

TABLE E1. (Continued)

ID	Age (y)	Sex	Type of cancer and stage	Drug	Symptoms of initial reaction	Brown's grade	Infusion number in which reaction appeared
87	68	F	Colon	Cetuximab	Rash and mild bronchospasm	II	1
88	62	F	Ovary	Doxorubicin	Rash and dyspnea	II	1
89	62	F	Pancreas	Irinotecan	Rash	I	11
90	56	F	Endometrium	Paclitaxel	Rash and abdominal pain	II	6

SpO₂, Peripheral capillary oxygen saturation.

TABLE E2. Skin test results, premedication and desensitization outcome

ID	Drug	Prick	IDT	Premedication	No. of desensitizations	Reactions	Outcome
1	Oxaliplatin	–	+	CCT, D	1	None	Stopped, progression
2	Cisplatin	–	+	CCT, D	3	Rash (I) on all 3 cycles	Completed
3	Oxaliplatin	–	–	CCT, D	9	None	Stopped, neuropathy
4	Docetaxel	–	–	CCT, D	4	None	Completed
5	Oxaliplatin	–	+	CCT, D	5	II (rash, mild bronchospasm) on cycle 5	Stopped, reaction
6	Paclitaxel	–	–	CCT, D	2	None	Completed
	Carboplatin	–	–	CCT, ASA 200, M, R	6	I en cycle 6	Completed
7	Oxaliplatin	–	+	CCT, D	14	None	Stopped, progression
8	Paclitaxel	–	+	CCT, D	15	None	Stopped, progression
9	Carboplatin	–	+	CCT, D	3	I on cycle 2 and II on cycle 3 (completed infusion)	Stopped, progression
10	Oxaliplatin	+	NP	CCT, D on cycles 1 and 2 plus ASA 500 mg, M, R since cycle 3	10	Grade I on cycles 1 and 2. None since cycle 3	Stopped, progression
11	Carboplatin	–	+	CCT, D	3	None	Completed
12	Carboplatin	–	+	CCT, D, M, ASA 200, R	2	None	Stopped, progression
13	Oxaliplatin	–	+	CCT, D	1	Rash (I), completed infusion	Stopped
14	Oxaliplatin	–	+	CCT, D, M, ASA 200, R	2	Rash (24 h later) in cycle 2	Stopped, neuropathy
15	Oxaliplatin	NA	NA	CCT, D, M, ASA 200, R	6	None	Completed
16	Docetaxel	NP	NP	ASA 200, M, R, D	1	None	Stopped, progression
17	Carboplatin	–	+	ASA 200, M, R, D	2	None	Completed
18	Cetuximab	NP	NP	ASA 200, M, R, D	13	None	Completed
19	Oxaliplatin	–	+	ASA 200, M, R, D	3	None	Completed
20	Paclitaxel	NP	NP	ASA 100, M, D, R	6	None	Completed
21	Docetaxel	NP	NP	ASA 200, M, D, R	2	None	Completed
22	Oxaliplatin	–	+	ASA 200, D, R	5	None	Completed
23	Paclitaxel	NP	NP	ASA 200, R, M, D	7	None	Completed
	Doxorubicin	NP	NP	ASA 200, R, M, D	3	None	Completed
24	Cetuximab	NP	NP	ASA 200, M, R, D	3	None	Stopped, progression
25	Oxaliplatin	–	–	ASA 200, R, D	6	None	Stopped, neuropathy
26	Oxaliplatin	–	+	ASA 200, M, R, D	8	None	Stopped, progression
	Cetuximab	NP	NP	ASA 200, M, E, D	3	None	Stopped progression
27	Oxaliplatin	–	+	R, D, hydroxyzine	4	None	Stopped, progression
28	Paclitaxel	NP	NP	ASA 200, M, R, D	14	Mild rash on cycle 1 (6 h later)	Stopped, progression
29	Oxaliplatin	–	–	ASA 200, R, D	5	None	Completed
30	Oxaliplatin	–	+	ASA 200, M, R, D	1	II en cycle 1 (stopped infusion)	Stopped, reaction
31	Carboplatin	–	+	ASA 200, M, R, D	1	None	Completed
32	Oxaliplatin	+	+	ASA 200, M, R, D on cycle 1, AAS 500 since cycle 2	4	II en cycle 1 (completed infusion), I (palm itching) en cycles 2-4	Stopped, progression
33	Paclitaxel	NP	NP	ASA 200, R, D	11	None	Completed
34	Paclitaxel	NP	NP	ASA 200, M, R, D	3	None	Completed
35	Paclitaxel	NP	NP	M, cetirizine, R, D	3	None	Completed
36	Oxaliplatin	–	+	ASA 200, M, R, D	4	None	Stopped, neuropathy
37	Oxaliplatin	–	+	ASA 200, M, R, D	6	None	Stopped, progression
38	Oxaliplatin	–	+	ASA 200, M, R, D on cycle 1, added ASA 500, and cetirizine since cycle 2	4	II on cycle 1 (completed infusion), I on cycle 2, none on cycles 3 and 4	Completed
39	Oxaliplatin	–	+	ASA 200, M, R, D, cetirizine	10	None	Completed

(continued)

TABLE E2. (Continued)

ID	Drug	Prick	IDT	Premedication	No. of desensitizations	Reactions	Outcome
40	Carboplatin	—	—	ASA 200, M, D, R	6	I on cycle 1	Completed
41	Paclitaxel	NP	NP	ASA 200, M, D, R	4	None	Completed
42	Carboplatin	—	—	ASA 200 (cycles 1-7), ASA 500 (cycle 8), M, D, R	8	II (moderate bronchospasm) on cycles 4 and 5, I on cycles 6 and 7 (all treatments were completed). None on cycle 8	Stopped, progression
43	Calcium folinate	—	+	ASA 200, M, R, D	4	Rash (I) on cycle 1, none on cycles 2 and 3	Completed
44	Docetaxel	NP	NP	ASA 200, M, R, D	7	None	Completed
45	Oxaliplatin	—	—	ASA 200, M, R, D	6	None	Stopped, neuropathy
46	Rituximab	—	—	Paracetamol, CCT, D	4	None	Stopped, toxicity
47	Rituximab	—	—	Paracetamol, D	1	II/unclear mechanism (hypertension, tachycardia) on cycle 1, stopped procedure	Stopped, reaction
48	Carboplatin	—	+	ASA 200, M, R, D	4	None	Completed
49	Doxorubicin	NP	NP	ASA 200, M, R, D	8	None	Stopped, myocardiopathy.
50	Oxaliplatin	—	+	ASA 200, cetirizine, R, D	5	None	Stopped, progression
51	Irinotecan	—	—	ASA 200, R, D	8	None	
52	Cetuximab	—	—	ASA 200, cetirizine, R, D, M	17	None	Completed
53	Paclitaxel	NP	NP	Cetirizine, M	2	None	Completed
54	Carboplatin	—	—	ASA 200, R, D	6	None	Stopped, progression
55	Pemetrexed	—	—	ASA 200, M, R, D, cetirizine	7	None	Stopped progression
56	Oxaliplatin	—	+	ASA 200, R, D	4	None	Completed
57	Oxaliplatin	—	+	ASA 500, M, D, R, cetirizine	5	None	Stopped progression
58	Rituximab	—	—	ASA 200, CCT, D, R, cetirizine, paracetamol	5	None	Completed
59	Paclitaxel	NP	NP	ASA 200, R, D	14	None	Continues
60	Cisplatin	—	+	ASA 200, R, D	2	None	Stopped, progression
61	Docetaxel	NP	NP	ASA 100, cetirizine, R, M, D	5	None	Completed
62	Paclitaxel	NP	NP	ASA 100, cetirizine, R, D	6	None	Stopped, progression
63	Carboplatin	—	+	ASA 200, D, R	4	None	Completed
64	Carboplatin	—	—	ASA 200, D, R	8	None	Stopped, progression
65	Oxaliplatin	—	—	ASA 200, D, R, cetirizine	2	None	Completed
66	Rituximab	—	—	CCT, R, D, paracetamol	5	None	Completed
67	Rituximab	—	—	CCT, R, D, paracetamol	8	None	Continues
68	Cisplatin	—	+	ASA 200, cetirizine, R, D	3	None	Completed
69	Oxaliplatin	—	+	M, D, R, ASA 200 since cycle 3	5	I in cycle 2	Stopped, progression
70	Carboplatin	—	—	ASA 200, R, D, cetirizine	6	None	Completed
71	Rituximab	—	—	ASA 200, CCT, R, D, paracetamol	1	None	Stopped, progression
72	Paclitaxel	NP	NP	ASA 200, M, D, R	4	None	Completed
73	Paclitaxel	NP	NP	ASA 200, M, D, R	5	None	Completed
74	Carboplatin	—	—	M, cetirizine, R, D	1	None	Stopped, progression
75	Oxaliplatin	—	+	ASA 500, R, D, cetirizine	8	None	Completed
76	Carboplatin	—	—	ASA 200, cetirizine, R, D	4	None	Completed
77	Oxaliplatin	—	+	ASA 200, cetirizine, R, D	5	None	Completed
78	Carboplatin	NP	NP	ASA 200, cetirizine, R, D	3	None	Stopped progression

(continued)

TABLE E2. (Continued)

ID	Drug	Prick	IDT	Premedication	No. of desensitizations	Reactions	Outcome
79	Oxaliplatin	—	+	ASA 200, cetirizine, R, D	3	None	Completed
80	Docetaxel	NP	NP	ASA 200, M, D, R	4	None	Stopped, progression
81	Oxaliplatin	—	+	ASA 200, cetirizine, M, D, R	3	None	Completed
82	Paclitaxel	NP	NP	ASA 200, M, R, D	16	None	Completed
83	Paclitaxel	NP	NP	D, R, M, cetirizine	2	None	Stopped, progression
84	Calcium folinate	—	—	ASA 200, D, R	11	None	Continues
85	Paclitaxel	NP	NP	ASA 200, cetirizine, R, D	8	None	Completed
86	Paclitaxel	NP	NP	ASA 200, cetirizine, R, D	7	None	Completed
87	Cetuximab	—	—	R, D, CCT.	1	None	Continues
88	Doxorubicin	NP	NP	R, D, CCT	1	None	Stopped, progression
89	Irinotecan	—	—	ASA 200, R, D, cetirizine	5	None	Stopped progression
90	Paclitaxel	NP	NP	ASA 200, R, D	1	None	Completed

ASA, Acetyl salicylic acid; CCT, corticosteroids (methyl prednisolone 1 mg/kg or hydrocortisone 100 mg); D, dexchlorpheniramine 6 mg ev; IDT, intradermal test; M, montelukast 10 mg; NA, nonassessable, cetirizine and hydroxyzine given orally twice a day on the 3 previous days, NP, not performed; R, ranitidine 50 mg ev.